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Long-Term Clinical Evaluation of Novel ECG Electrodes

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Abstract

Atrial fibrillation is an intermittent disease that causes irregular heart rate and eventual atrial myocardium exhaustion. The standard silver / silver-chloride (Ag/AgCl) hydrogel electrode is sensitive to moisture and becomes more susceptible to motion artifacts that reduce electrocardiogram (ECG) signal quality. FLEXcon USA© has developed a moisture-independent and less-expensive electrode design that can improve short- and long-term clinical ECG measurement. Ten subjects were recruited for two clinical studies. The first quantified the long-term biocompatibilities and adhesion strengths of the FLEXcon and hydrogel electrodes during seven days; the Gen. 2-A adhesive experienced 7.14% adhesion loss, whereas the hydrogel experienced 50% adhesion loss. The second study utilized heart rate variability analysis to quantify ECG quality during four days. The correlation coefficients between heart rates measured by the FLEXcon and hydrogel electrodes while the subjects were at rest and in motion were both 0.997. The acquired results demonstrate that the FLEXcon adhesive and the industry standard hydrogel produce statistically similar ECG signals in short- and long-term clinical applications.

Chapter 1: Introduction

During the past decade, the population and average lifespan in the United States have increased. The improved quality of life has resulted from advancements in the medical field and improvements in health care. However, health care expenditures have increased proportionally with the growing demand for medical treatment of the elderly and injured. In 2009, hospital care and physician services together constituted more than 50% of the $2.330 trillion nationally spent on health services, whereas 6.3% was allocated for medical instrumentation and in-home treatment (American Hospital Association, 2011). The average cost of a hospital stay was $9,700 in 2010 (Pfuntner et al, 2013), and for many, only a small fraction of these expenses were covered by medical insurance.

Various diagnostic medical procedures, such as cardiac monitoring and sleep studies, require the patient to stay in the hospital during the day or overnight. The allocations of medical professionals and patient care space are sources of inpatient expenses, regardless of the resulting diagnosis. However, medical engineering has innovated diagnostic hospital care by producing handheld and wearable diagnostic devices that the patient can use without admission to a hospital. The ability to easily measure physiological health factors, such as blood glucose content, educates the patient to maintain his or her health at home and prevent medical emergencies.

Although several biological factors can be measured with portable medical instrumentation, some of these factors, like cardiac health, still require the analysis of a physician. The electrocardiogram (ECG) is the measurement of electrical cardiac activity and is acquired by the placement of electrodes on the skin. This electrical signal correlates to the nervous and muscular actions that occur during a heartbeat. Abnormal heart function is reflected

by changes in the neuromuscular function and ECG — some changes such as escalated heart rates are easily observable, but other conditions like mitral valve prolapses and long QT syndrome require a trained professional's diagnosis. The development of portable and handheld ECG monitoring devices that can acquire, process, and store the electrical signal has allowed physicians to monitor the vital signs of post-surgery patients outside of the hospital. However, the quality and accuracy of the ECG are reliant on the performance of the primary sensing unit, the ECG electrode, and have a significant impact on the physician's ability to diagnose cardiac abnormalities.

The Silver/Silver Chloride (Ag/AgCl) hydrogel electrode is the modern gold standard of ECG sensing. Composed of a high-moisture hydrogel medium that prevents contact between a conductive metal disk and the patient's skin, these sensors utilize an electrolytic, semi-liquid medium that facilitate low-impedance electrical signal transfer from the skin surface. Although this electrode system increases sensitivity to electrical cardiac signals with moisture, the gel-like layer dries out over time, increasing skin-to-electrode friction and causing significant ECG measurement distortions.

To improve long-term sensor performance, FLEXcon USA© has produced an electrode that does not require quickly-drying gels to measure the ECG from the skin surface. This electrode design uses a patented Pressure Sensitive Adhesive (PSA) doped with conductive compounds to promote high surface area skin-to-electrode adhesion. These electrodes require electrophoretic activation prior to clinical use, due to biocompatibility regulations established by the Association for the Advancement of Medical Instrumentation (AAMI), to ensure that the internal sensor impedance remains less than 2 kΩ. Last year's Major Qualifying Project (MQP) designed a method by which to evaluate the compliance of the FLEXcon electrode with AAMI

standards and the electrical short-term performance versus that of the standard Ag/AgCl electrode.

This year, the current MQP group designed and conducted a method of clinically comparing long-term FLEXcon and Ag/AgCl electrode performances. This procedure addressed the numerous obstacles of physical and electrical interactions between the electrode and the skin, such as skin-to-electrode adhesion, repositionability, skin irritation, and ECG signal quality. The collaboration with FLEXcon to develop a biocompatible, strongly adhesive, and signal-receptive ECG electrode design will provide a means of ensuring high-quality, long-term, and in-home vital sign monitoring of post-surgery cardiac patients.

Chapter 2: Literature review

2.1 Bio-potential Electrodes

Bio-potential electrodes have an important role in medical instrumentation for the measurement of physiological signals. Electrodes are made with metals or inert materials, which are not toxic to biological tissue and are mechanically strong and have good conductivity for detecting electrical signals generated by the body. There are different electrodes for different applications that are used in clinical settings today. Types of physiological signal measurement encompass: Electroencephalography (EEG) for receiving electrical activity of the brain; Electroneurogram (ENG) for receiving electrical response from Peripheral muscles; Electromyogram (EMG) for receiving electrical contraction of the muscles; Electroretinogram (ERG) for receiving the electrical signal of the retina in the eyes; and Electrooculogram (EOG) for measuring the position of the eyes.

Electrodes are made in different shapes for different applications. Figure 5 shows an electrode that is used in the clinical field is made from silver/ silver chloride (Ag/AgCl) surrounded by a gel-coated sponge for better conductive electrical signal. The hydrogel electrode is the industry standard of noninvasive ECG measurement in clinical settings but relies on moisture for signal acquisition. During long-term applications, the loss of moisture reduces ECG trace quality, primarily due to friction and air insulation. Monitoring intermittent cardiac anomalies requires constant ECG measurement over the span of multiple days.

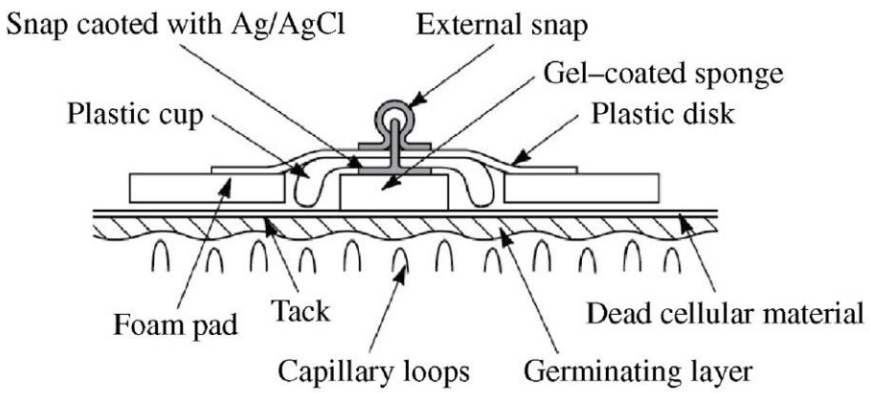


Figure 1: Typical electrode with all components.

There are two types of electrodes: Ag/AgCl and dry electrodes. The advantage of the Ag/AgCl electrode is the quality of the signal, however they dry out quickly; therefore, they have to be replaced frequently and are not suited for long-term monitoring. Ag/AgCl electrodes are also expensive.

Novel Dry ECG electrodes are made from compositions of carbon and pressure sensitive adhesive (PSA). Figure 6 shows two main types of electrodes, which FLEXcon is developing.

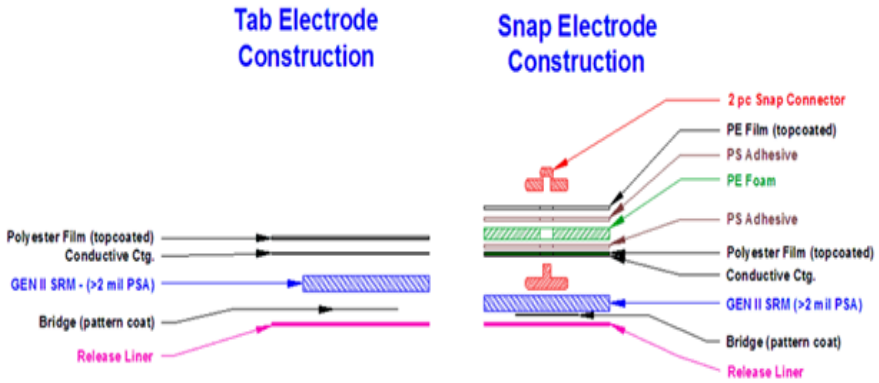


Figure 2: Dry Electrodes Types Provided by FLEXcon.

Dry electrodes have the potential of replacing the hydrogel electrodes, however they also have some disadvantages. The last year's MQP team found some minor problems that needed to

be overlooked for a solution to the signal distortion on long term monitoring. In other words, based on their conclusion, the dry electrodes have a silver plate on top which could shift due to the movement of the patient. The use of the dry electrodes in many cases resulted in puncturing of the skin, therefore the use of this method does not facilitate long-term monitoring –scar tissue grows around the puncture and increase the impedance of the skin. Since there is a tight bond between the skin and the dry electrode there will be moisture in the surface and the impedance will decrease.

2.2 Relevance of the ECG to Clinical Settings

Clinical settings, such as hospitals, guarantee proper and effective patient care with physiological measurements that characterize the patient's vital signs. During perioperative stages of patient treatment, biological sensors translate vital sign-derived properties, like blood pressure and cardiac conduction, into displayable and analyzable quantities and signals. From the measured signals, trained medical professionals can determine and monitor the patient's health in real-time during invasive and non-invasive procedures. The electrocardiogram (the signal generated by the attachment of electrodes to the skin) is utilized in various medical situations to serve as a supplemental or primary method of cardiac function characterization.

The ECG can provide electrical information about cyclical cardiac motions and contractions. This signal can be correlated to results produced by other methods (such as imaging and energy expenditure measurements) to characterize heart function in complex environments. To clinically evaluate ventricular function in strenuous environments such as exercise, external forces exerted by human subjects onto a cycle ergometer can be correlated to cardiac contraction that is simultaneously shown by magnetic resonance imaging (MRI) (Gusso *et al*, 2012). Because the images are generated at a specific frequency, the MRI has no significant meaning

unless each image is mapped to a time-dependent cyclical heart function. The ECG is used in conjunction with these two devices to provide a time-dependent relationship between the degree of cardiac contraction and the periodic nature of cardiac conduction and blood transport (Fratz *et al*, 2013). The incorporation of the ECG demonstrates how modern methods that relate heart function to physical stresses and activities require accurate and noninvasive means of heart rate measurement.

Although clinical studies have demonstrated that there is a direct correlation between muscular and cardiac activities, some medical conditions can cause sudden cardiac stresses that can be reflected by the ECG combined with blood pressure, blood composition measurements. The concurrent use of several vital sign monitoring methods is required to quickly treat a patient experiencing sudden physiological instability because a variety of environmental factors could contribute to a single medical condition; therefore, the rapid discovery of each contributing factor directly contributes to the quick and accurate diagnosis and treatment of the patient's complication. Analyzing arterial blood samples can determine the presence of metabolic and nutritional maladies that can be treated with specific medications (Baugher and Mattu, 2011). Simultaneously observing the ECG of the patient can suggest whether specific aortic, ventricular, and myocardial disorders are affecting cardiac function. If these cardiac disorders are caused by arterial blood transfer abnormalities or vice versa, the physician can use these two or more diagnostic measurements to accurately diagnose the patient. The ECG is important for in-hospital diagnoses of patient-specific cardiac ailments, but additional physiological measurements are necessary to determine the appropriate treatment due to the interconnected nature of the digestive, immune, respiratory, circulatory, and reproductive systems.

2.3 Clinical Measurement of the ECG

When used in conjunction with other diagnostic processes in a clinical setting, the ECG can provide valuable information about the patient's health. To detect the patient's ECG, electrodes are primarily used. These sensors are attached to specific regions of the patient's skin to detect ionic propagation from the heart to the skin surface and translate the ionic movement to electronic current through the electrode body. This electrical current is then processed and stored in an acquisition device and subsequently displayed on a monitor to show the ECG to the physician. Each step of this clinical ECG signal acquisition process – skin preparation, electrode placement, and signal transmission – requires an array of considerations that contribute to a reliable and accurate representation of the patient's cardiac activity.

2.3.1 Skin Preparation

Prior to the utilization of cardiac sensors in a clinical setting, a variety of procedures could be performed to cleanse the patient's skin. The human dermis is supported by blood vessels and periodically regenerates layers of cells to replace the death of outer-surface epidermal cells (due to a lack of epidermal blood vessels), causing a superficial layer of dead, compressed, and shedding cells to rest on the skin. This layer slightly increases the overall thickness of the skin, consequently increasing the impedance – resistance to the transmission of electrical current – from the underlying musculature and nerves to the surface electrode (Oster, *Proper Skin Prep*). The thickening of the skin layer and high impedance are ultimately responsible for offset voltages and decreased signal-to-noise ratios (SNRs) in the ECG signal. Therefore, minimization of the dead skin layer is vital for ensuring ECG quality and facilitating subsequent clinician analysis.

2.3.2 Electrode Placement

Following skin preparation, the electrodes need to be placed on the skin to detect the propagation of electrical cardiac signals within the body. The locations and number of electrodes used to measure the ECG depend on the application. In clinical practices, the main standard electrode configurations are 3-lead, 5-lead, and 12-lead measurements. As more electrodes are connected to the patient, more ways of depicting cardiac function are available to analyze, altogether helping provide a more comprehensive diagnosis (Barill, 2003). Ideally, the electrodes are placed on the chest because of the proximity to the heart. However, electrodes can also be attached to the arms and legs, but larger motion artifacts (due to frictional between the electrode and skin) will be present in the signal. The variety of reliable configurations allows the clinician to decide how detailed the ECG must be to detect specific cardiac irregularities; for obvious discrepancies in the waveform that characterize easily discernible diseases, fewer electrodes are required to detect that abnormality.

2.3.3 Signal Transmission

Measurement of the ECG can be accomplished in the hospital and at the home. The nature in which the ECG must be measured determined what kind of apparatus must be used to collect and store the signal. For stationary measurements, large machines can be used to receive, store, and digitally process the data with a detailed user interface. However, longer-term measurements often involve patients or subjects moving around and require a smaller, lightweight signal-storing apparatus. Clinical studies that correlate dietary habits and cardiac function utilize mobile ECG systems to collect the cardiac signals while subjects perform everyday tasks (Yamakoshi *et al*, 2013). The development of mobile ECG systems has equipped biomedical research with a means of characterizing heart function in dynamic environments.

2.4 Clinical Diagnosis of Cardiac Abnormalities

After the acquisition and filtering of the ECG signal, the physician can observe the signal to detect abnormalities. Various cardiac dysfunctions cause characteristic transformations in the ECG signal. Irregularities such as atrioventricular block and ventricular arrhythmias cause delayed electrical signal transmission from the atrioventricular node to the purkinje fibers that control ventricular contractions). This pumping of blood from the atria into the ventricles corresponds to the ECG R-wave. Therefore, the delay in blood transfer to the ventricles is reflected by a normal P-Q wave complex that is separated from a delayed R-wave by a prolonged pause (Yodogawa *et al*, 2007). Other abnormalities, such as mitral valve prolapse, can affect an entire complex of waves in the ECG. In the 3-lead configuration, the slight backflow of blood from the ventricle back into the atrium through the slightly open mitral valve causes an inverted T-wave and an elevated S-T wave complex in the ECG (Manenti *et al*, 2013). Changes in the ECG waveform can show how any cardiac disease may alter the ECG signal substantially; this signal transformation allows the clinician to easily diagnose and treat the patient immediately, preventing severe injury or death.

2.5 Clinical Evaluation of Electrode Performance

Because the electrode is the primary sensor used to measure the ECG, the physical properties of the sensor determine how well the signal is recorded. The ability of an electrode to adhere strongly to the skin surface determines the quality of the signal. When the adhesion between the electrode and the skin is stronger, the isolation of the skin-to-electrode interface is increased, and environmental interference is reduced (Cömert, Honkala, and Hyttinen, 2013). There are various ways to quantify and describe the adhesion and biocompatibility of these skin-adhesive biological sensors.

Electrode-to-skin adhesion can be quantified by various quantities. Devices that measure force, pressure, torque, and shear can be used to accurately simulate peeling motions with high precision (Murakami *et al*, 2012). A more qualitative approach is the use of clinical feedback. After peeling the electrode from the skin, subject can complete a survey (0 – 10) that evaluates how much pain the person felt. Higher perceived pain corresponds to increased adhesion (Austin and Patel, *Considerations*). In clinical studies, the utilization of mechanized instruments increases measurement capabilities at the expense of financial cost, whereas simple qualitative tests are easier to perform with greatly diminished accuracy and resolution. Therefore, a balance of mechanical and subject-feedback tools should be utilized together to provide a detailed description of surface-to-surface adhesion.

Analogous adhesion measurements, the evaluation of skin irritation can be conducted qualitatively or quantitatively. The most widely used qualitative assessment is the use of a survey that asks whether the patient has experienced epidermal allergies such as itchiness, dryness, or scaling (Boyce, Kelliher, and Vallande, 2000). Alternatively, the measurement of skin capacitance can be used to characterize skin swelling and water content, both of which are symptoms of oedema. When the skin is exposed to an irritant, the fluidic retention of the epidermis increases. Because the degree of swelling is proportional to the degree of water retention, ultrasonic devices can be used to determine the thickness of the skin and correlate that thickness to the degree of irritation (Miettinen *et al*, 2006). In clinical studies, a combination of qualitative surveys that document sensations and devices that measure skin water retention can fully characterize human skin reactions to applied adhesives.

2.6 Digital Signal Processing

The ECG sensor output is an electrical analog signal that is transmitted in real-time. However, this signal is generally not ideal or perfect, due to background noise, motion artifacts, and offset voltages. Modern apparatuses utilize analog components to receive the signal that is transmitted from the electrodes through wire leads. Because printed circuit boards and microprocessors are becoming more efficient and less expensive, digital filtering and signal correction is utilized by analog-to-digital conversion techniques. The use of digital filtering is more efficient than analog filtering because analog circuits are heavily impacted by temperature changes, whereas digital components can sample the real-time signal, store the data (which cannot be corrupted by ambient temperatures), and perform rapid computations.

Embedded signal processing has incorporated much more software-based operations to minimize the need for additional analog parts. The hardware is designed to convert and store the data, and the software allows the engineer or physician to control how the data is processed. In the clinical setting, a variety of digital filtration algorithms in these user interfaces help the physician perform quick and reliable analyses of ECG waveform data. To detect arrhythmia, the signal is filtered to remove noise, artifacts, and voltage drift to improve signal detail. Then, changes in the QRS wave complex of the ECG (the periodic global signal maximum) are detected with a threshold algorithm (Kim *et al*, 2011). The QRS complexes of these filtered signals are then expressed in the frequency domain (as a mixture of sinusoidal waveforms). The signal magnitude profile has a lower frequency (slower rate of cardiac depolarization) than that of a healthy ECG signal if arrhythmia is affecting the patient. The ability to characterize the rate at which cardiac function is changing is an important result of fast and compact embedded signal processing with minimal instrument variability.

Digital processing reduces component costs, minimizes device weight, and facilitates high-level analyses and computations. The incorporation of embedded algorithms in hardware for specific disease detection mechanisms minimizes the time required for computations; the rapid passage of information through these software circuits serves as a signal filtration method with a negligible time-lag that is comparable to real-time analog signal processing. In the emergency room, where patient health can quickly decline during invasive surgery, the high precision and minimal response time of digital ECG-processing systems help surgeons and physicians keep the patient alive and stable.

Chapter 3: Project Strategy

3.1 Initial Client Statement

The initial client statement was proposed by FLEXcon to the MQP team on September 11, 2013:

"Starting with prior ECG MQP, update Test Protocol Methodology based on Association for the Advancement of Medical Instrumentation (AAMI) for evaluating long term use of electrodes. Perform 2 design of experiment (DOE) processes to determine synergistic effect of electrode performance which including signal quality and susceptibility to interference. Report results using this technique. Product recommendations (compared to hydrogel ECG control) based on analysis (constrained within limits of the given design). Recommendations on what to improve based on their understanding of the application requirements."

3.2 List of Objectives

The team carefully read the client statement and consulted with its advisor, Professor Chon. The team was able to identify six desirable characteristics of the design method. The first objective the team found was long-term ECG measurement. This objective is the main goal of the company. By talking to the sponsors and advisor, we defined a long term measurement time frame as 7 or fewer days, which is within the regulations of Associations for Advancement of Medical Instruments (AAMI). The second objective was safety because the team needs to consider the health of each human subject in order to avoid inhumane means of data acquisition. Safety for human subject will include limiting skin irritations, accounting for allergies, and preventing electrical shock from the testing instruments. The third objective was the comparison of novel ECG electrodes with hydrogel electrodes. The comparison of both electrodes will require proper skin preparation and the performance of electrodes in long and short term measurements. Also, the electrodes will be compared based on storage in extreme conditions

prior to use. The fourth objective is signal processing. Means of developing mathematical algorithms are important for facilitated calculation of heart rate and signal noise. The ability of the two electrode types to measure these parameters will facilitate the comparison of electrode performance. The fifth objective is comfort of the ECG electrodes on the human subjects. The well-being of the subject is important because this design method must not interfere with his or her daily activities and ensure that the subject behaves naturally during the experiment. The final objective is minimum instrumentation and subject cost because the equipment has to be reliable, the subject have to be given proper incentives to follow the experimental protocol.

Table 1: Pairwise comparison of project objectives.

	Minimum instrumentation and subject cost	Comfort	Safety	Long-term measurement	Comparison of novel and hydrogel electrodes	Signal Processing	Total
Minimum instrumentation and subject cost	XXX	0.5	0	0	0	0	0.5
Comfort	0.5	XXX	0	0	0	0.5	1
Safety	1	1	XXX	0.5	0.5	1	4
Long-term ECG measurement	1	1	0.5	XXX	0.5	1	4
Comparison of novel and hydrogel electrodes	1	1	0.5	0.5	XXX	0	3
Signal Processing	1	0.5	0	0	1	XXX	2.5

3.3 List of Constraints

Because the subject must act naturally and perform his or her personal daily routines, the instrumentation must weigh less than 1 pound. Also, the length of these clinical trials cannot last longer than seven days because AAMI regulations prohibit overly strenuous experimental conditions. This seven day period mimics the longer time period of inpatient ECG monitoring in hospital facilities. The number of recruited subjects and the amount of compensation are constraints because we want to minimize the expenses that are used by this method but require a sufficient amount of data to show the performance of the electrodes. For this procedure, we have a limited number of ECG data storage devices to distribute to subjects, which limits the number of subjects that can be monitored at a given time.

3.4 Revised Client Statement

After the definition and clarification of our objectives and constraints, we sought to define how the Design of Experiments should be made to accomplish the objectives and stay within the limitations of the constraints. Therefore, our revised client statement encompassed the following tasks:

- *Design a clinical study that abides by AAMI regulations to measure the SRM-to-skin adhesion, repositionability, skin irritation, and moisture resistance of three novel ECG electrode designs (and a standard hydrogel electrode) over the course of 7 days.*
- *Based on the results of the first clinical study, design a second clinical study that will compare the electrocardiogram signals acquired from a single novel electrode design and a standard hydrogel electrode over a period of 7 days.*
- *Develop a method of digital signal processing that will reduce background noise without causing signal distortion. This processing system must be applied to the ECGs acquired by the novel and standard electrodes.*
- *Recommend what to improve based on the group's understanding of the application requirements*

3.5 Project Approach

Based on the revision of the client statement, this project comprises three main goals: evaluate the short-term and long-term physical properties of novel and Ag/AgCl electrodes; measure the short-term and long-term electrical signals transmitted by novel and Ag/AgCl electrodes; and process the acquired signals to compare the overall performance of both electrode types. To accomplish these three goals, the group developed a three-stage project design each stage or phase will accomplish an individual goal and determine how the next stage

will be conducted. Phases I and II are primarily clinical studies that must be designed to produce data, whereas Phase III is a digital system that must be designed to process the collected data.

The first phase of the project is the evaluation of physical properties (skin adhesion, repositionability, and skin irritation) that characterize the performance of FLEXcon's novel electrodes and the traditional Ag/AgCl electrodes. Prior to experimentation, we need to help FLEXcon design the composition of electrode substrates (the material that composes the backing of the tab electrode) to determine 3 testable, flexible electrode designs. Within this phase, this study must encompass the design of a simple, user-friendly, and safe method of measuring the peeling force required to remove electrodes from the skin. This test is meant to evaluate the repositionability of each electrode type and replicate clinical, in-hospital scenarios in which electrodes have to be repositioned due to human error. In this phase, a second experiment has to be conducted simultaneously to evaluate skin irritation every 24 hours. Although electrodes are meant to be disposable, we need to determine how signal integrity changes over longer periods of time and test long-term performance during in-home diagnostic medical procedures.

The second phase uses the results from Phase I to select a single experimental electrode design to test, versus the traditional hydrogel electrode. Two experiments will be run in parallel to measure (1) the long-term ECG and (2) the ECG signal quality versus short-term repositioning. In this phase, we need to design methods of measuring the ECG of the subjects during the day and store the data without impeding everyday activities.

Lastly, Phase III will be conducted to design a digital filtering system that will compare the ECG signals recorded from the two electrode types. Measuring heart rate, motion artifacts, and other quantities will complete this comparison.

3.5.1 Financial Project Management

The group and its advisor discussed feasible remuneration quantities with which to compensate subjects. To decide an exact quantity, we had to determine which quantity would give enough incentive to follow a 7-day, day-to-day procedure, come to the lab for an initial 1-hour session, and return every 24 hours for diagnostic and data-collecting 20- minute sessions. We concluded that $200 for the participation in this 7-day study would be sufficient to guarantee compliance. Therefore, if we need a total of 20 subjects for Phases I and II a total of $4,000 will be needed for adequate remuneration. Also, to make sure that our protocols conform to AAMI regulations, we need to purchase up-to-date documentation ($190). The Biomedical Engineering Lab and our advisor will provide Holter monitors and other ECG monitoring software.

Lastly, we need to determine how many electrodes will be used throughout the study. Below, we have constructed a table that shows how many electrodes will be required to conduct all of our clinical studies.

Table 2: Calculation of projected electrode count required to complete both clinical studies.

Phase	# of subjects	# of electrode types tested	# of electrodes of each type	Total number of electrodes used	Total Electrode Cost
1	10	4	2 + 7	360	?
2	10	2	3 + 3	120	?

Based on these calculations, we cannot immediately determine how much these custom experimental electrodes will cost. However, we know that we will require a total 400 experimental electrodes (360 + extra). Based on online market prices, we estimated that 100 Ag/AgCl electrodes (60 + extra) will be required, yielding a total expense of approximately $26.

Clinical Experimentation Design Evaluation Matrix (Design of Phases I and II): A comparison of macro-scale clinical study designs that emphasize the overall recruitment and equipment feasibility.

Table 3: Numerical Evaluation Design Matrix utilized to determine feasibility of subject recruitment.

Objectives (O)and Constraints (C)	200 subjects, 50 subjects for each of 4 experiments	20 subjects, 10 per phase (I and II), Use of Bio-Pak ECG system	40-subject recruitment, 10 subjects for each of 4 experiments, Mobile Holter ECG Monitors	20 Subjects, 10 per phase (I and II), Mobile Holter ECG monitors
Lightweight instrumentation (c)		X		
Complies with AAMI standards (c)				
Minimizes # of subjects (c)				
Minimizes number of subjects (c)	X			
safe (O)			100	100
Long-term ECG measurement (O)			100	100
Comparison of Novel and AgCl (O)			100	100
Signal Processing (O)			70	90
Comfort (O)			90	80
Minimize instrumentation cost (O)			50	80

Table 4: Gant Chart of planned project progress throughout the academic year.

Gant Chart	Term A					Term B						Term C					Term D			
Weeks	1	3	5	7	Week 8: off	1	3	5	7	16-Dec	16-Jan	1	3	5	7	Week 8: off	1	3	5	7
•Background																				
•Design Phases 1 and 2																				
•Complete and submit IRB																				
•Subject recruitment for Phase 1																				
•Conduct Phase 1 Experiments																				
•Design Phase 3																				
•Subject recruitment for Phase 2																				
•Conduct Phase 2 Experiments																				
•Process Phase 2 results with Phase 3																				
•Final report and presentations																				

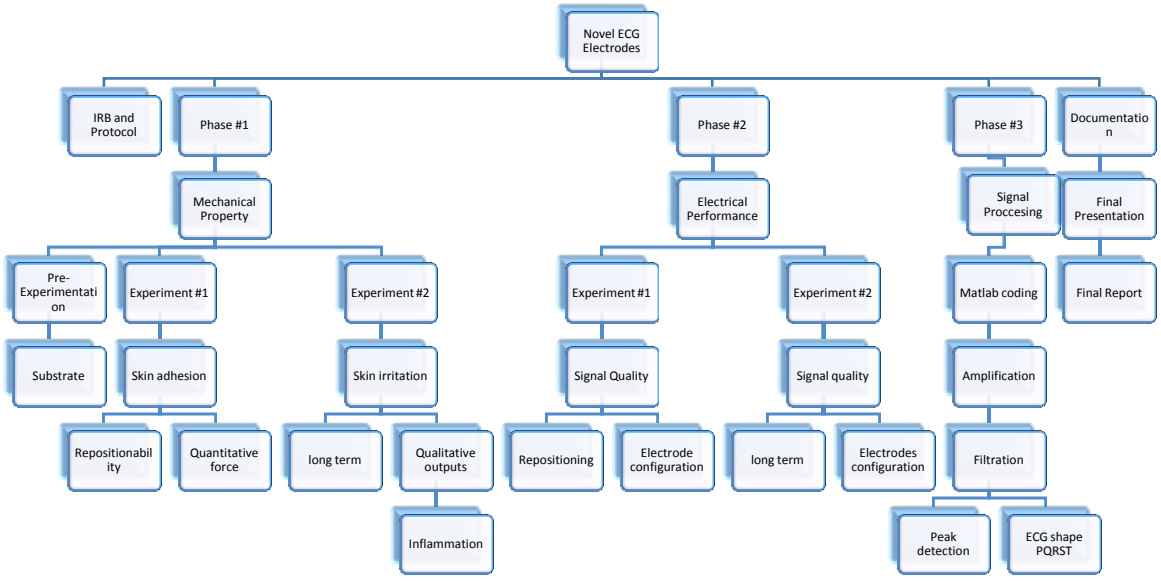


Figure 3: Work breakdown structure for planning of two clinical studies and subsequent signal processing.

Table 5: Function and Means Table utilized to suggest feasible methods of completing the main objectives of all three phases.

Functions	Means								
Measure skin irritation	Capacitive skin moisture retention	Subject feedback survey	European skin prick test	OET irritation potential test	Draize irritation potential test				
Measure skin adhesion	Force Transducer	Pressure Transducer	Shear transducer	Torque Transducer	Gravity				
Store ECG signals	Desktop computer hard drive	Mobile Laptop	External hard drive	Holter monitor	Bio-Pak system				
Analyze / process ECG signals	Analog components	Microprocessor (C programming language)	MATLAB	Band-pass filter	Notch filter				

Chapter 4: Project Design Process

4.1 Introduction

Based on the revision of the client's statement, the group developed a list of design requirements that could guide the formulation of a clinical study that will assess the physical properties of experimental electrode adhesives. Before designing the clinical study, the group was responsible for selecting the electrode body material to which each adhesive could be attached. The design of the electrode body material will be used to maintain the integrity of the adhesive by providing structural support and sufficient flexibility. By minimizing environmental interference, the electrode body will allow the clinical study to effectively compare the FLEXcon adhesives' interactions with skin to those of a standard hydrogel.

4.2 Needs Analysis

Next, a clinical study must be designed to meet specific requirements to produce reliable results. The primary functional needs of the clinical study are safety and long-term evaluation capabilities. These two requirements were ranked equally because jeopardizing the health of the subjects would eliminate the integrity of any long-term data, and the ability to collect long-term data is important for interpretation of the client's electrode performance.

The two major goals of this clinical study are: the evaluation of physical skin irritation every 24 hours, for seven days; and the measurement of adhesion strength between FLEXcon's electrodes and human skin, to a precision of 0.1 N. Also, this study must allow us to measure the subject's ECG continuously over 4 days.

The major limitations of the study are electrode size and instrumentation weight. Because this study is meant to replicate the conditions used in long-term clinical monitoring, the shape and size of the tested electrodes must be comparable to those produced in the medical industry.

Also, minimizing the weight of heart rate monitoring instrumentation is important for improving subjects' comfort. The group determined that collection of two sets of ECG data should require no more than 2 pounds of equipment.

4.3 Procedure and System Designs

4.3.1 Electrode Body Material Design

The design of the electrode body was a major design component with a focus on stress-dependent moduli, such as maximizing resistance to shear stresses; maximizing tensile resistance; and maximizing flexibility. To prevent erosion of the material, the electrode body must be chemically resistant to salt and fresh water, weak acids, and weak alkali that are secreted on the surface of the skin.

CES EduPack, a database of modern materials, was utilized to generate a list of possible electrode body materials and compare their physical properties.

As shown in Table 6, eleven different materials were selected for a comparison of chemical stabilities. The skin secrets sweat that contains extremely small concentrations of alkaline and acidic compounds; a majority of its composition is sodium and chloride dissolved in water (Fukumoto et al, 1988). Therefore, the resistances of each material to weak acids and alkali, fresh water, and salt water were analyzed and compared. This database used a scale in which a value of zero signified little to no durability in response to exposure to a specific type of substance, and a value of five represented high resistance to the specified compound.

Table 6: CES EduPack descriptions of material durability ratings during exposure to compounds of varying acidity.

	Durability	Durability	Durability	Durability	Durability	Total Durability	Suitable?
material	Weak Acids	Weak alkali	salt water	fresh water	UV		(Y / N)
PTFE	5	5	5	5	4	24	Y
LDPE	3	3	3	3	1	13	N
LDPE	3	3	3	3	1	13	N
HDPE Foam	3	3	3	3	2	14	N
HDPE Foam	3	3	3	3	2	14	N
PP	5	5	5	5	1	21	Y
PP Foam	5	5	5	5	1	21	Y
PE Foam	3	3	3	3	1	13	N
Polyester	3	0	5	5	4	17	N
PVC Elastomer	5	5	5	5	2	22	Y
PVC Semi-rigid	5	5	5	5	4	24	Y

A summation of the resistance values was calculated for each of these eleven materials, and the five materials with the greatest scores were selected for a secondary comparison. This secondary comparison was utilized to select a material that could provide sufficient mechanical structure to an attached adhesive in reaction to force loading. As shown in Table 7, the Young's Modulus characterized resistance to tension and stretching; the flexural modulus described material response to bending, and the shear modulus explains material reactions to shear forces. These moduli, in addition to the threshold strengths of the stress-strain curves, were considered in the selection of electrode substrate materials.

Table 7: Descriptions of material resistances to shear, tensile, compressive, and flexural stresses.

		Material Name				
Material Property	Units	PTFE	PP	PP Foam	PVC Elastomer	PVC Semi-rigid
Max Density	(lb/in^3)	0.0795	0.0328	0.000795	0.0403	0.0191
Min Young's Mod.	(Msi)	0.058	0.195	0.0000435	0.0000872	0.0653
Min Comp. Mod.	(Msi)	0.0583	0.195	0.00228	0.0000872	0.0593
Min Flex. Mod.	(Msi)	0.0779	0.19	0.0000435	0.0000872	0.102
Min Shear Mod.	(Msi)	0.02	0.0743	0.0000145	0.0000292	0.0245
Min Yield Str.	(ksi)	2.86	4.77	0.00653	0.872	0.725
Min Tensile Str.	(ksi)	3	4.78	0.0348	1.08	1.31
Min Comp. Str.	(ksi)	1.62	5.87	0.00653	1.05	0.725
Min Flex. Str.	(ksi)	4.2	4.34	0.00653	2.42	2.61
Min Shear Str.	(ksi)	N/A	N/A	0.00326	0.862	0.363
Elongation	(%)	200-400	168 - 598	12.0 - 15.0	357-392	28-32
Max Water Abs.	(%)	0.01	0.0205	1.5-1.9	0.635-0.772	0.8-1
O2 Perm.	(cm^3/(1000m*day*atm)	218-363	58.3-99.7	N/A	3600-4810	N/A

4.3.2 Skin Irritation Experiment Design

In Phase I of the clinical study, five different types of ECG electrodes were tested on ten human subjects. FLEXcon provided four experimental adhesive compositions: Generation 1 (Gen. 1), Generation 2 (Gen. 2), Generation 2-A (Gen. 2-A), and Generation 3 (Gen. 3). The fifth adhesive was the Ag/AgCl hydrogel that is utilized as an industry standard in hospital settings today. The team's objectives were the testing of all five types during a seven-day trial, the collection of data from each type, and the analysis of the collected data to determine which FLEXcon adhesive was as biocompatible and mechanically stable as the standard hydrogel. The best-performing FLEXcon adhesive was subsequently tested in a second clinical study (Phase II) that measured signal quality.

By monitoring each subject each day for a period of one week, we were able to distinguish the severity of skin irritation in each subject, and determining the best performing ECG electrodes during long-term monitoring. The long-term biocompatibility experiment was designed to recruit a diverse subject population with a variety of skin types. The skin type and ethnicity of each subject is listed in Table 8. The different types of skin that were chosen would provide a comprehensive understanding of the effect of irritation, but also simulate a real life clinical setting.

Seven electrodes of each type were placed in rows, as shown in Figure 9, on each subject's forearms. Each day, one electrode of each adhesive type was removed, and the skin was carefully examined for signs of irritation, such as redness or discoloration. After the daily procedure was complete, the individual was given two different questionnaires, which were related to discomfort, irritation and itchiness experienced in the past 24 hours. This survey was then processed in excel for later analysis of each type of electrode.

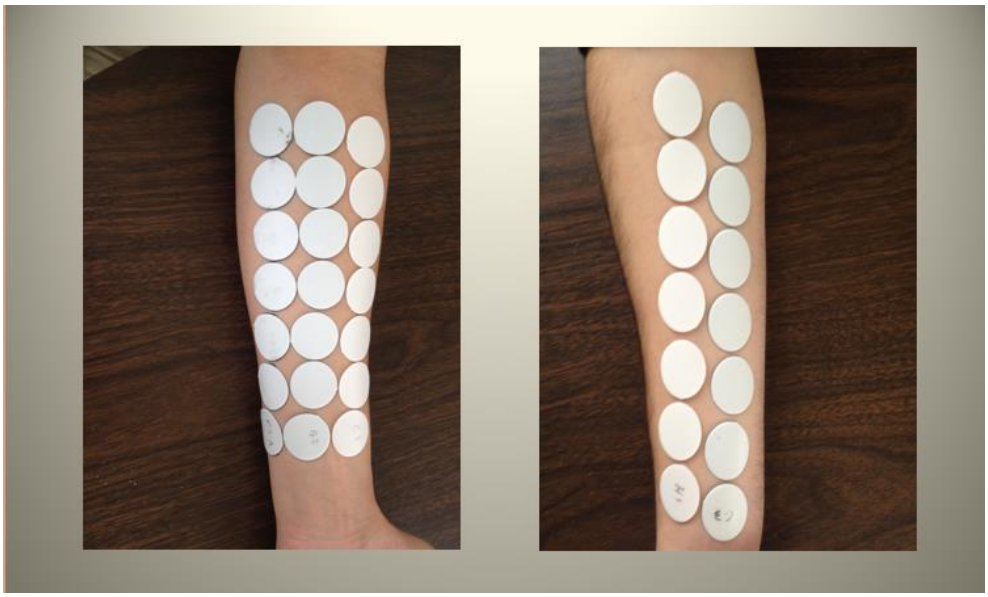


Figure 4: Electrocardiogram electrode placement inside the forearms.

Table 8: Demographic information (Skin moisture content and ethnicity) of each subject who volunteered to participate in the Phase I studies.

	Subjects									
	Subject #1	Subject #2	Subject #3	Subject #4	Subject #5	Subject #6	Subject #7	Subject #8	Subject #9	Subject #10
Ethnicity	Hispanic	East EU	East EU	East EU	Hispanic	West EU	S. Asian	Afr. American	West EU / Hispanic	E. Asian
Skin Type	Moderate	Dry	Dry	Moderate	Moderate	Moderate	Dry	Oily	Moderate	Oily

4.3.3 Removal Force Experiment Design

The first clinical study procedure has to apply tension to the center and edges of electrodes and provide precise force measurements.

For force measurement and application, there is no limitation of instrumentation weight or dimensions. However, the utilized device must allow us to control peeling velocities and angles as well as provide precise force measurements in real time. A study has demonstrated that peeling forces required to remove clinical adhesives from patients' skin have magnitudes of less

than 5 Newton's (N) (Murahata, Taylor, Damia, Houser, and Grove). Therefore, the group decided that a precision of 0.1 N was needed to sufficiently characterize the peeling force profile. The evaluation of adhesive resistance to lead wire pulling forces requires capabilities of measuring larger tensile strengths. Another study demonstrated that the force acting on the electrode body is experienced by the attached wire, causing lead retention as large as 50 N (Coggins, 2010). Therefore, the clinical study would have to include methods of measuring a wide range of tensile forces.

Table 9: Function means chart describing alternative methods of applying tensile force and connecting a force transducer to the electrode body.

Functions	Means								
Exert Force	Spring	Manual	Hydraulic Machinery	Weights / gravity					
Connect Transducer to Electrode	String	Clamp	Wire	Adhesive					

After selecting tensile force as a descriptive measure of adhesive strength, the group discussed multiple modes of tensile force application as well as a variety of connections between the electrode body and the transducer.

Each method of force application has its own benefits and disadvantages. A spring system would allow the group to precisely measure the displacement of the spring and quickly calculate the potential energy (and force magnitude) required to remove the electrode from the

skin; however, the spring could break if it is too weak, or the release of the spring recoil immediately after electrode removal can injure the subject.

Hydraulic or high-powered machinery would provide a precise and steady control of peeling rate, but the components are often expensive, heavy, and require extensive training prior to use. The short project timeline would cause restrictions on resource and assistance availability.

Weight suspension can guarantee adjustable peel angle and facilitated force measurement based on mass; however, the weights themselves have very low precisions in mass measurement. Because the tested adhesives are experimental, their strengths have not been tested. Therefore, measuring the necessary force to remove the electrode from a substrate by incrementing the applied mass at larger intervals would prevent the group from determining whether the weight is exactly or above the adhesive strength threshold.

A manual pulling motion can serve as an alternative method of tensile force application. Manually applying tension will allow the group to control peeling angle, rate, and force magnitude easily; however, neural control of muscular contraction causes fluctuations in contractile force steadiness. Motor neurons stimulate two types of skeletal muscle, slow-twitching (Type I) and fast-twitching (Type II), at rates of 10-20 Hz and 30-60 Hz, respectively. The combination of these stimulations allows the muscle to quickly provide large forces (using the Type II fibers, which contract and relax quickly) and sustaining that force magnitude (with the Type I fibers, which contract and relax slowly) in tetanus contraction (Webster 144-146). The mechanical force profile reflects the fluctuation of force exertion with peaks upon fiber contraction (propagation of electrical signals into the neuromuscular junctions) and valleys upon relaxation (the temporal gaps between neural stimulation).

Next, the group brainstormed a list of possible methods of attaching the force application source to the electrode body. The advantages and drawbacks of string, clamps, wires, and glues were analyzed.

The main advantages of string and wire are their flexibilities. In the design of the clinical study, peel angle must be controlled or adjusted to simulate the overall force vector of a clinical, manual peeling motion. However, at higher tensile stresses, the string can stretch or break. The failure of the string during an experiment can waste materials and hamper experimental processes if the removal force is greater than the string's yield stress. Securing the string or wire to the electrode would require tying it around the metal electrode tab for central pulling motions and threading through a hole in the electrode edge for peeling motions. Although the string and wire would be easy to remove, altering the electrode body would increase the likelihood of tearing the electrode tab because the loop would apply constrictive forces along the tensile force's directional vector.

Adhesives could be used to bond the transducer to the electrode body. Therefore, the mechanical adhesion between the two subtracted would be stronger. Although the mechanical stability of the system would be increased, the electrode cannot be interchanged easily with another. The ability to disengage the transducer from the electrode in a facilitated fashion is important for transducer calibration between force measurement trials.

A clamping mechanism would provide a different approach to attaching the transducer to the electrode body with a grasping action. This method replicates the grip that human hands use to peel an electrode by its tab, pressing on both sides of the tab to cause compression normal to both the direction of the pull and the plane of the electrode tab.

4.3.4 Signal Processing Algorithm Design

The signal processing of the raw data was done by using the programing language MATLAB. The code was designed to process the ECG signals. Before starting to write the code for signal processing, it was needed to know that the Holter monitor save data in discrete time and the sampling frequency is 180 samples per second. Based on the sampling frequency, the code was design to detect all peaks of ECG signal. The code includes loading the data, sampling frequency and time vector. Next, a series of filters (band-pass, derivative, and moving average) were utilized to remove noise from the ECG signal and locate R waves. The gains of these filters (Equations 1 – 7) were derived from the literature, as provided by (Pan and Tompkins, 1985). The last part of the peak detection was the selection of the threshold that was applied to the output of the moving average filter. This threshold established index-based peak-searching domains that defined the plausible locations (in time) of QRS complexes.

First, the raw data of ECG saved from all the subject are loaded to the program by using the code below. The code below shows an example for loading data saved form Holter monitor and BIOPAC system.

```
%% Read data
data = load ('S8_R1.txt');    % Load data collected with Biopac system
fc = data(:,2);     %FLEXcon electrode data in second column, in Volts
ag = data(:,1);     %Ag/AgCl electrode data in first column, in Volts
data1 = load ('3-fc-d3-e.csv'); % Load data collected with Holter
fc = data1(:,3);    %FLEXcon electrode data uses channel 3, in Volts
data2 = load ('3-ag-d2-e.csv'); % Load data collected with Holter
ag = data2(:,3);     %Ag/AgCl electrode data uses channel 3, in Volts
fc= fc(1:24000);     %Specified range of data for FLEXcon
ag= ag(1:24000);     %Specified range of data for Ag/AgCl
```

```
% All FLEXcon variables began with "fc" and Ag/AgCl variables with "ag"
```

The load function on Matlab imports all data into a matrix MxN, where N is the number of rows and M is the number of columns. The text file have a matrix 2xN which first column is Ag/AgCl data and second column is FLEXcon data. The csv file has 3 columns which are three channels of Holter monitor.

Second, sampling frequency which was specified by the sampling frequency of the instrumentation used during ECG measurement (200 or 180 Hz). Also this code finds the duration of the entire data and returns the time in seconds and plot the raw data.

```
%% The Number of Samples per 1 second and
                  %the duration of the signal with time vector
%Fs=200;  % Biopac system sampling frequency
Fs=180;   % Holter monitor sampling frequency
dt=1/Fs;  % time step between each sample
duration=length(fc)*dt; % the duration of data in seconds (2 minutes)
t=0:dt:duration-dt; % The vector of time
t=t';   % it changes the columns to rows
```

Next, this part of the code removes all DC noise which caused by movement of the subjects. After, the code plots both ECG signals on same plot with a legend as it is shown on figure below.

```
%% Remove the DC noise of the signal
fc=fc-mean(fc); %FLEXcon signal
ag=ag-mean(ag); %Ag/AgCl signal
%% Plots the Raw data after removing DC noise.
figure(1)
```

```
plot(t,fc); % Plots FLEXcon signal
grid on; hold on;
plot(t,ag, 'r-.');  % Plots Ag/AgCl signal
xlabel('Time [s]');
ylabel('Voltage [V]');
title('Raw ECG Waveform');
legend('FLEXcon','AgCl');
```

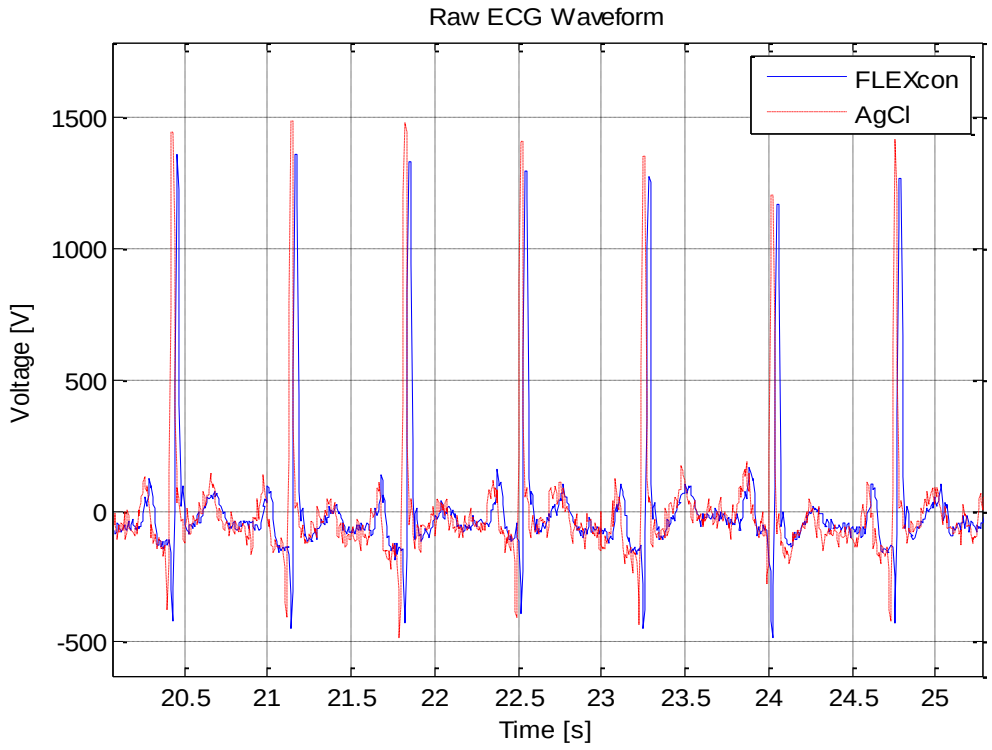


Figure 5: FLEXcon signal and Ag/AgCl signal after the removal of DC noise

Fourth, this part of the code is very important part of the signal processing. This part is band-pass filter which was constructed by using low-pass filter and high-pass filter. The signal goes first in low pas filter and then in high-pass filter. The cut off frequencies for band-pass filter are 5 Hz for low frequency and 11Hz for high frequency. This band-pass filter removes the power line interference of 60 Hz.

The low pass filter algorithm was design from the transfer function of the second – order as it is shown in equation 1. The difference equation of this equation 1 is shown in equation 2 which is low pass filter that pass low frequencies from 0 to 11Hz.

Equation 1: $$H(z) = \frac{(1-z^{-6})\text{^}2}{(1-z^{-1})\text{^}2}$$

Equation 2: $$Y(nT) = 2y(nT-T)-y(nT-2T)+x(nT)-2x(nT-6T)+x(nT-12T)$$

The high pass filter algorithm was driven from first order transfer function which is shown in equation 3. The difference equation was founded from the transfer function of equation 3 is shown in equation 4. This difference equation is high pass filter which passes all frequencies above 5 Hz. The band-pass filter was crated from equation 2 and 4 with cut off frequencies 5 Hz and 11Hz.

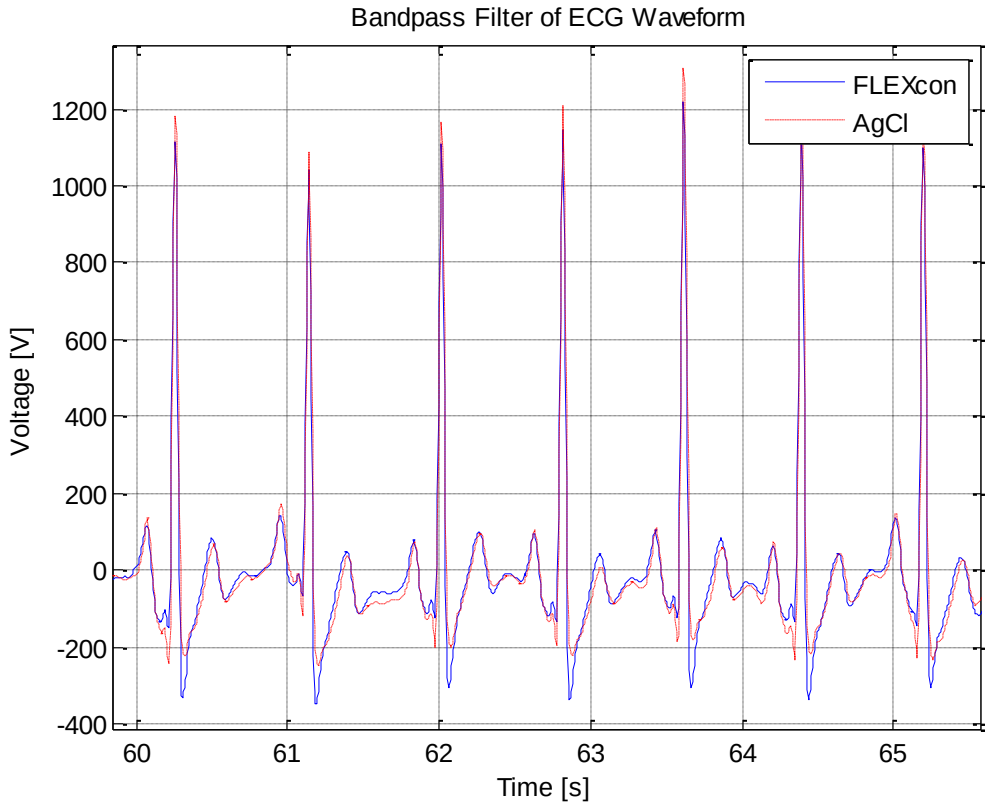
Equation 3: $$H(z) = \frac{(-1+32z^{-16}+z^{-32})}{(1+z^{-1})}$$

Equation 4: $$Y(nT) = 32x(nT-16T)-[y(nT-T)+x(nT)-x(nT-32T)]$$

```
%% Low-pass filter
bl=[1 0 0 0 0 0 -2 0 0 0 0 0 1]; % Coefficients b of the difference
%equation of lowpass filter
al=[1 -2 1]; % Coefficients a of the difference equation of low-pass
%filter
fc_lp=filter(bl,al,fc); %FLEXcon low-pass filter
ag_lp=filter(bl,al,ag); %Ag/AgCl low-pass filter

%% High-pass filter
```

```
bh=[-1 zeros(1,15) 32 zeros(1,15) 1]; % Coefficients b of the
%difference equation of high-pass filter
ah=[1 1]; % Coefficients a of the difference equation of high-pass
%filter
fc_hp=filter(bh,ah,fc_lp); %FLEXcon high-pass filter
ag_hp=filter(bh,ah,ag_lp); %Ag/AgCl high-pass filter
figure (2)
plot(t,fc_hp); %FLEXcon signal after band-pass filter
grid on; hold on;
plot(t,ag_hp, 'r-.'); %Ag/AgCl signal after band-pass filter
xlabel('Time [s]');
ylabel('Voltage [V]');
title(' Bandpass Filter of ECG Waveform');
legend('FLEXcon','AgCl');
```



Fifth, after filtering the signal, it is needed to take the derivative of the signal and then square it. This provides only positive values and accentuates larger values. This manipulation made it easy to detect peaks and their time locations. This was the best way to get higher accuracy of peak detection. The transfer function used for the derivative used 5 points which had transfer function as is shown in equation 5 and the difference equation 6 was derived from equation 5.

Equation 5: $$H(z) = (1/8T)(-z^{-2} - 2z^{-1} + 2z^{1} + z^{2})$$

Equation 6: $$y(nT) = \left(\frac{T}{8}\right)[-x(nT-2T) - 2x(nT-T) + 2x(nT+T) + x(nT+2T)]$$

```
%% Derivative filtering, squaring
bd=(1/8)*[2 1 0 -1 -2]; % Coefficients b of the difference equation of
derivative function
ad=[1]; % Coefficients a of the difference equation of derivative
function
fc_der=filter(bd,ad, fc_hp); %FLEXcon derivative filter
ag_der=filter(bd,ad, ag_hp); %Ag/AgCl Derivative filter
fc_sq=(fc_der).^2; %FLEXcon, signal squared of derivative
ag_sq=(ag_der).^2; %Ag/AgCl, signal squared of derivative
```

After utilization of the derivative filter, moving average filter was used for both signals. This code helped to set up the threshold which all the R-peaks are above it. The threshold was set below of all the R-peaks which made it easy to find them all without losing any peak. The moving average difference equation is shown in equation 7. Threshold was set after the moving average filter and it was set by the algorithm provided below.

Equation 7: $$y(nT) = \left(\frac{1}{N}\right)[x(nT-(N-1)T) + x(nT-(N-2)T)T) + \cdots + x(nT)] \quad (7)$$

```
%% Moving average filter
N=30; % Moving average filter length
bm=(1/N)*[ones(1,N)];
am=[1];
fc_m=filter(bm,am,fc_sq); %FLEXcon Moving Average filter
ag_m=filter(bm,am,ag_sq); %Ag/AgCl Moving Average filter
%% Thresholds set by the mean of MA signal
thr_fc= mean(fc_m); %Threshold for FLEXcon
thr_ag= mean(ag_m); %Threshold for Ag/AgCl
fc_p=zeros(size(fc_m));%Set all values below threshold to zero, FLEXcon
ag_p=zeros(size(ag_m));%Set all values below threshold to zero, Ag/AgCl
fc_p(find(fc_m>=thr_fc))=1; %All values above threshold are 1 FLEXcon
ag_p(find(ag_m>=thr_ag))=1; %All values above threshold are 1 Ag/AgCl
```

Finally, the code below finds all the peak located above the threshold with specific time location and make a mark on R wave of the ECG signal. After all the peaks are found, they were counted and then computed the heart rate which was given in beats per minute's BPM. All the peaks for FLEXcon are marked with circle "o" and Ag/AgCl peaks are marked with star "*".

```
%% searches for peaks between rising edges and falling edges
a1=diff(fc_p); %Derivative of square signal, FLEXcon
a2=diff(ag_p); %Derivative of square signal, Ag/AgCl
upindex_fc=find(a1==1); %Rising edges for FLEXcon
upindex_ag=find(a2==1); %Rising edges for Ag/AgCl
downindex1=find(a1==-1);%Falling edges for FLEXcon
downindex2=find(a2==-1); %Falling edges for Ag/AgCl
%% FLEXcon, peak detection
```

```
prev_peak_fc=0;
for i=1:min(length(upindex_fc),length(downindex1))
[amp1,indtemp1]=max(fc_hp(upindex_fc(i):downindex1(i)));
indmax1(i)=indtemp1+upindex_fc(i)-1;
rpeak_fc(i)=t(indmax1(i));
bpm_fc(i)=60./(rpeak_fc(i)-prev_peak_fc);
prev_peak_fc=rpeak_fc(i);
end
%% Ag/AgCl, peak detection
prev_peak_ag=0;
for i=1:min(length(upindex_ag),length(downindex2))
[amp2,indtemp2]=max(ag_hp(upindex_ag(i):downindex2(i)));
indmax2(i)=indtemp2+upindex_ag(i)-1;
rpeak_ag(i)=t(indmax2(i));
bpm_ag(i)=60./(rpeak_ag(i)-prev_peak_ag);
prev_peak_ag=rpeak_ag(i);
end
%% Peak Detection plots
figure(6)
plot(t, fc_hp)
hold on; grid on;
plot(rpeak_fc, fc_hp(indmax1),'or');
xlabel('Time (s)');ylabel('Voltage after BP filtering (V)');
title('FLEXcon ECG Waveform')
figure(7)
plot(t, ag_hp,'k')
hold on; grid on;
plot(rpeak_ag, ag_hp(indmax2),'xr');
xlabel('Time (s)');ylabel('Voltage after BP filtering (V)');
```

```
title('Ag/AgCl ECG Waveform')
```

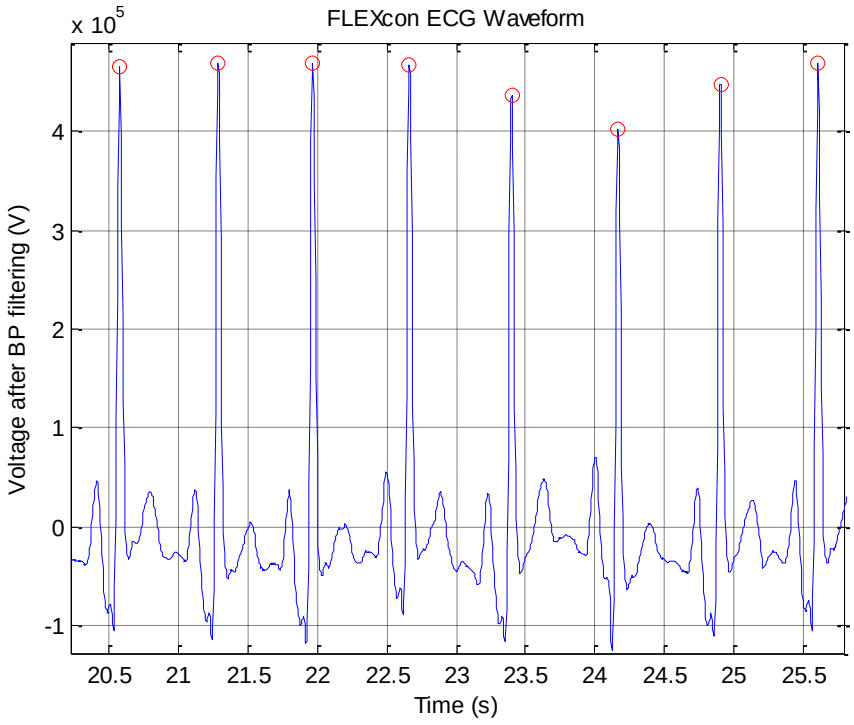


Figure 6: FLEXcon Band-Pass ECG with Overlaid Peak Detection.

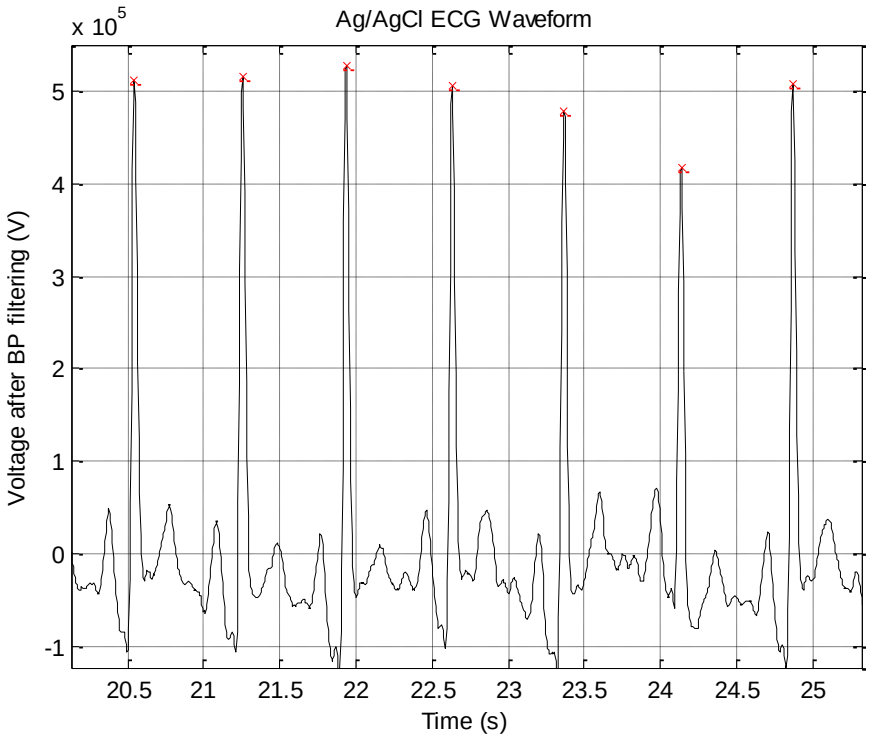


Figure 7: Ag/AgCl Band-Pass ECG with Overlaid Peak Detection.

```
%% Cubic interpolation of R-R interval
RR_fc=diff(rpeak_fc); %Difference in time between R-R intervals,
FLEXcon
RR_ag=diff(rpeak_ag); %Difference in time between R-R intervals,
Ag/AgCl
time_lr_fc=zeros(1,length(RR_fc));
time_lr_ag=zeros(1,length(RR_ag));
time_lr_fc(1)=0;
for i=2:length(RR_fc)
time_lr_fc(i)=sum(RR_fc(1:i-1));
end
time_lr_ag(1)=0;
for i=2:length(RR_ag)
time_lr_ag(i)=sum(RR_ag(1:i-1));
end
timeRR_fc=0:1/4:sum(RR_fc)-1/4;
timeRR_ag=0:1/4:sum(RR_ag)-1/4;
ys_fc=interp1(time_lr_fc,bpm_fc(1:length(time_lr_fc)),timeRR_fc,'spline
');
ys_ag=interp1(time_lr_ag,bpm_ag(1:length(time_lr_ag)),timeRR_ag,'spline
');
ys_fc= ys_fc-mean(ys_fc);
ys_ag= ys_ag-mean(ys_ag);
```

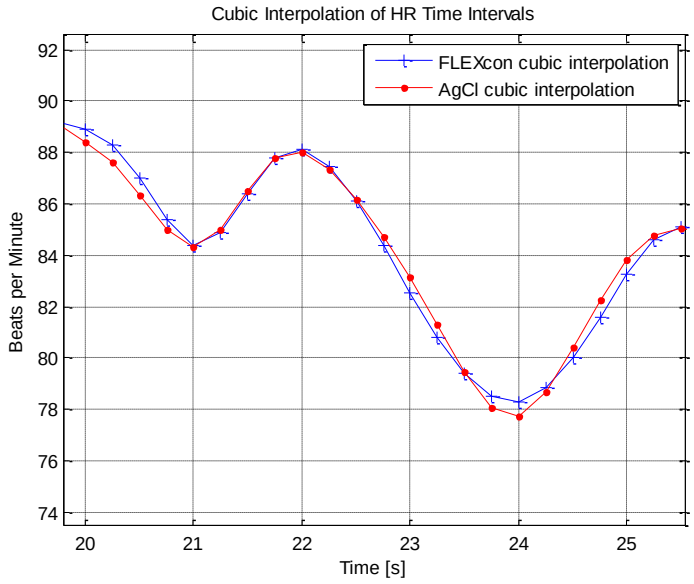


Figure 8: Cubic Interpolation of Heart Rate.

```
%% Power Spectral Density (PSD)
[psd_cubic_fc,f]=pwelch(ys_fc,length(ys_fc),[],512,4); %PSD, FLEXcon
[psd_cubic_ag,f]=pwelch(ys_ag,length(ys_ag),[],512,4); %PSD, Ag/AgCl
psd_cubic_fc=(abs(psd_cubic_fc)).^2;
psd_cubic_ag=(abs(psd_cubic_ag)).^2;
```

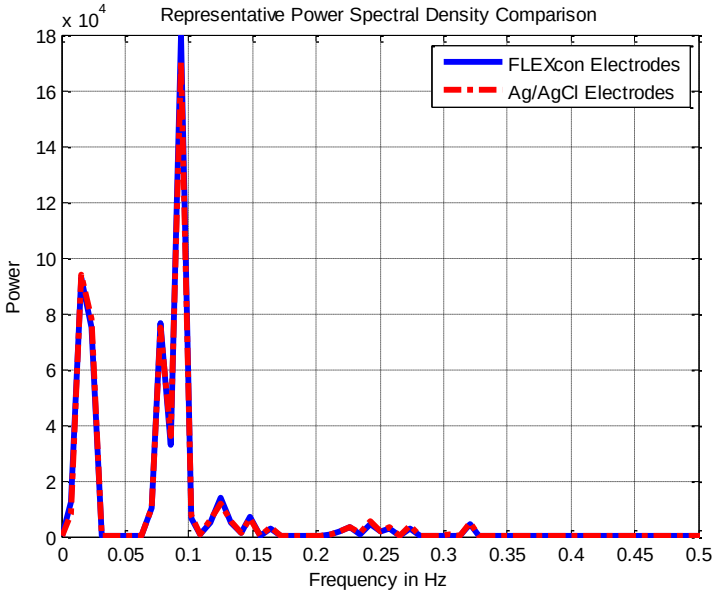


Figure 9: Power Spectral Density.

4.4 Conceptual Design of Clinical Studies

4.4.1 Phase I Design

Note: Experiment 1 and Experiment 2 are run in parallel from subject to subject

Subjects (on whom to perform Exp's 1 and 2): 10

1. Give a clinical study informational form for the subject to read and sign; obtain informed consent from the subject
2. **Conduct standard pre-ECG measurement skin preparation

For each of the 4 tested electrode types:

Experiment 1: Measuring repositionability and skin adhesion as a function of removal force

3. Place two electrodes on the inside forearm and record the time and date of electrode positioning.
4. After electrode placement, wait 10 seconds. Then, using a string connecting the electrode edge or center to a weight, measure the force required to peel one electrode by the edge and measure the force required to pull the second electrode by its center
5. Record the required forces and reposition the electrodes on the same region of the skin.
6. Repeat steps (4) and (5) 8 times or until the peeling / pulling forces are too small to measure.
7. Following the completion of measurements, remove these 2-electrode sets from the forearms. Conduct post-experiment skin sanitation procedures.

Experiment 2: Measuring long-term biocompatibility

1. Place 7 FLEXcon electrodes (per electrode type) on the subject's chest and record the date and time of electrode application.
2. Every 24 hours:
    a. Remove an electrode of each type from the subject and observe the degree of skin irritation.
    b. Photograph the skin that was in contact with the removed electrode.
    c. Non-invasively measure the skin impedance of the skin.
    d. Ask the subject to complete a portion of a survey to describe any discomfort or irritation experienced within the past 24 hours.
3. Following the completion of measurements, conduct post-experiment skin sanitation procedures.

4.4.2 Phase II Design

Number of subjects: 10 (do not have to be the same subjects tested in Phase 1, but a variety of skin types is still required).

**Based on optimal Electrode iteration (1 design), test the varied storage conditions versus ECG quality of a single experimental electrode

1. Give a clinical study informational form for the subject to read and sign; obtain informed consent from the subject

Experiment 1: long-term ECG signal

2. Perform standard pre-ECG measurement skin preparation

3. Place 3 Ag/AgCl electrodes and 3 FLEXcon electrodes on the subject's thorax and chest to measure the 3-lead ECG signals.
4. Have the subject wear two Holter monitors around the waist; one records the FLEXcon electrode signals, and the other records the Ag/AgCl electrode signals.
5. Power on all electronics and make sure that all components are functional. Record the date and time of electrode application.
6. After initial device activation, ask the subject to sit on a chair in the laboratory for 10 minutes.
7. Make sure that all the electronics are recording the ECG properly; after the 5 minutes of ECG acquisition, the subject can continue his or her daily activities.
8. Before going to sleep or taking a shower, the subject must turn off the Holter monitor. Then, he or she must remove the Holter monitor and its leads but keep the electrodes attached to the skin.
9. After waking up or taking a shower, the subject must re-attach the Holter monitor and its leads to the electrodes. Then, he or she must turn on the Holter monitor.
10. Every 24 hours:
    a. The subject must come back to the laboratory and repeat steps 6 and 7.
    b. The subject must complete a portion of a survey to describe any discomfort or irritation experienced in the past 24 hours.
11. Following the completion of measurements, remove these 3-electrode sets from the chest and collect the ECG monitoring instrumentation from the subject. Conduct post-experiment skin sanitation procedures.

Experiment 2 (Performed in parallel to Experiment 1): ECG signal versus repositioning

1. Ask the subject to sit on a chair in the laboratory and relax.
2. Conduct proper clinical skin preparation prior to ECG electrode placement.
3. Place an Ag/AgCl electrode and a FLEXcon electrode on the subject's inside forearms and lower abdomen to measure 3-lead ECG signals.
4. Connect the electrodes to the BIOPAC ECG collection system, initiate the system, and measure the subject's ECG for 30 seconds.
5. Measure the subject's ECG for 6 minutes.
6. Keeping the leads attached to the electrodes and continuing to have the BIOPAC system measure signals, remove each electrode from the skin for 10 seconds and then place them back on the original application sites.
7. Repeat steps (5) and (6) 8 times or until the electrodes are no longer able to adhere to the skin.
8. Following the completion of measurements, remove these 3-electrode sets from the forearms and abdomen. Conduct post-experiment skin sanitation procedures.

Chapter 5: Results

5.1 Phase I: Electrode Adhesion Statistics

Every 24 hours, the number of electrodes that fell off of each subject's arm was recorded in order to quantify electrode-to-skin adhesion. Once the total number of electrodes was determined, the charts were constructed using excel. The crucial fall off period of each type of electrode was the first four days of monitoring. These first four days gave accurate measurements of electrode fall off rates. The tally of electrode loss (organized by electrode adhesive type) is illustrated in Figures 10 and 11.

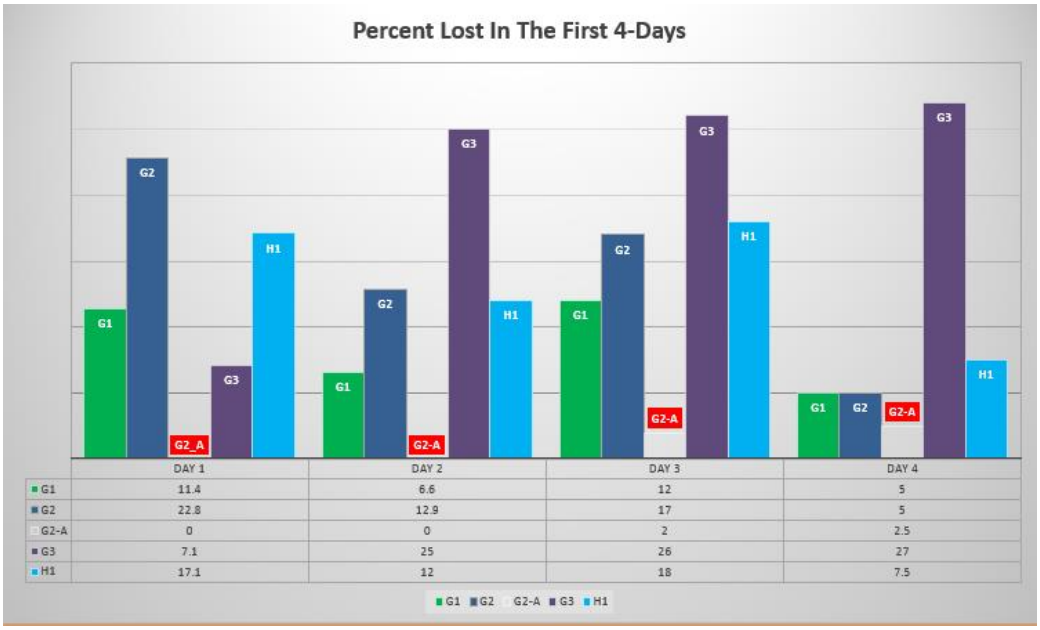


Figure 10: Percent fallen off electrocardiogram electrodes in the first 4-days of the testing.

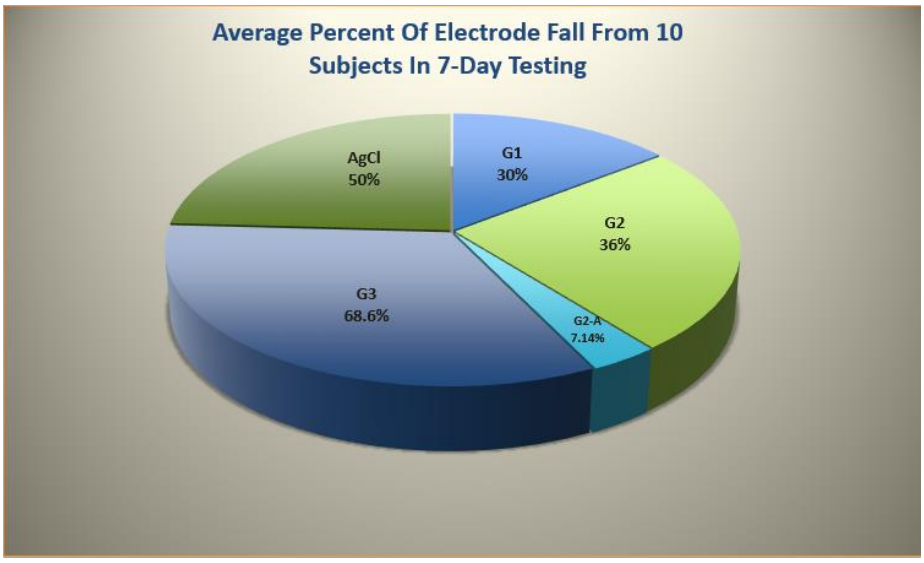


Figure 11: Average percent of ECG electrodes that had fallen during 7-Day testing from 10 Subjects.

5.2 Phase I: Removal Force Data

The measurement of adhesion forces was designed to quantify the mechanical strength of an adhesive produced by FLEXcon and a standard hydrogel adhesive. The control hydrogel electrodes consisted of a central AgCl electrode sponge surrounded by an adhesive layer, whereas FLEXcon's adhesive served as both a signal-receptive medium and an adhesive layer. These measurements of peeling forces and pulling forces were utilized to determine how the addition of a signal-transmitting functionality changes the adhesive strength of the compound.

Table 10: Measured peak pulling forces for each of 10 subjects during the first (F1) and second (F2) removals of each electrode type.

	Electrode Description	Subject #1	Subject #2	Subject #3	Subject #4	Subject #5	Subject #6	Subject #7	Subject #8	Subject #9	Subject #10	Average	STDEV
		(N)	(N)	(N)	(N)	(N)	(N)	(N)	(N)	(N)	(N)	(N)	(N)
A1_F1_Pulling	AGCL RIGID	24.1	16.8	20.7	19.2	18.6	15.1	20.4	15.0	11.7	29.7	19.1	5.1
A1_F2_Pulling	AGCL RIGID	3.3	8.8	3.6	8.7	5.7	5.3	4.4	7.1	7.8	5.3	6.0	2.0
A2_F1_Pulling	AGCL SOFT	23.3	25.8	28.8	8.7	9.2	8.1	15.9	16.9	17.1	29.1	18.3	8.2
A2_F2_Pulling	AGCL SOFT	3.6	5.3	2.0	3.7	3.7	4.1	2.6	9.5	8.0	11.2	5.4	3.1
B1_F1_Pulling	FLEX RIGID	14.7	28.9	34.0	21.5	10.4	21.6	26.5	26.4	20.9	26.3	23.1	6.9
B1_F2_Pulling	FLEX RIGID	3.6	4.2	2.0	3.9	4.5	4.0	2.4	2.6	4.3	13.9	4.5	3.4
C1_F1_Pulling	FLEX SOFT	3.5	12.6	22.3	25.4	11.1	18.3	18.6	20.5	14.9	18.0	16.5	6.3
C1_F2_Pulling	FLEX SOFT	3.2	3.8	2.7	3.6	2.7	3.4	2.3	4.7	3.9	5.7	3.6	1.0

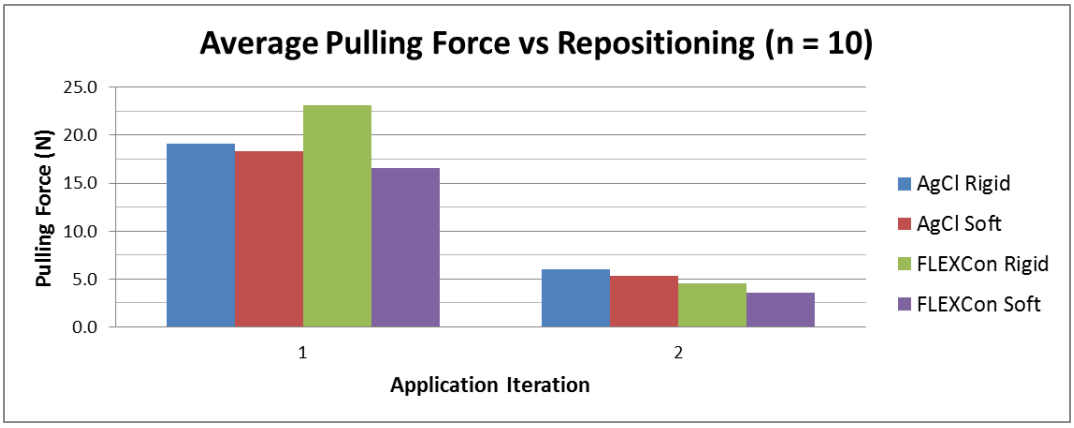


Figure 12: Average maximum pulling force required to remove each electrode type.

Fig. 13a. Fig. 13b.

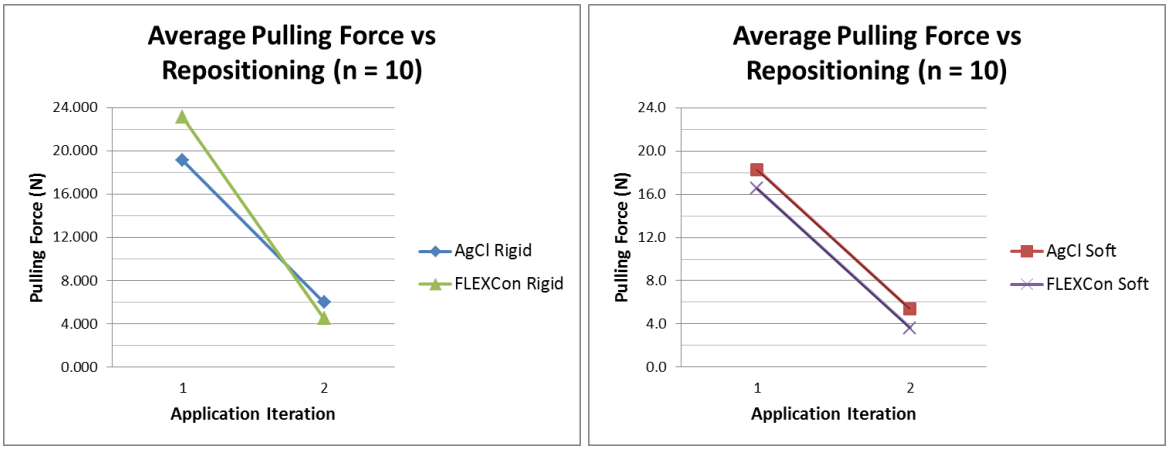


Figure 13: Comparison of adhesion loss between the control and FLEXcon adhesives after repositioning, with (a) foam and (b) fabric body materials.

Table 11: Measured peak peeling forces for each of 10 subjects during the first (F1) and second (F2) removals of each electrode type (in response to pulling forces).

	Electrode Description	Subject #1	Subject #2	Subject #3	Subject #4	Subject #5	Subject #6	Subject #7	Subject #8	Subject #9	Subject #10	Average	STDEV
		(N)	(N)	(N)	(N)	(N)	(N)	(N)	(N)	(N)	(N)	(N)	(N)
B3_F1_Peel	AGCL RIGID	1.399	1.476	2.415	1.956	1.920	1.515	1.566	1.287	1.596	2.927	1.8	0.5
B3_F2_Peel	AGCL RIGID	0.394	1.017	0.718	0.872	0.508	0.519	1.097	1.113	0.868	1.244	0.8	0.3
B2_F1_Peel	FLEX RIGID	1.484	2.230	1.849	3.323	0.848	1.475	1.414	2.812	1.460	1.500	1.8	0.7
B2_F2_Peel	FLEX RIGID	0.180	0.444	0.357	0.323	0.346	0.656	0.510	0.809	0.430	0.345	0.4	0.2
C2_F1_Peel	FLEX SOFT	1.127	0.758	1.645	0.792	0.638	0.918	0.602	1.132	0.709	1.229	1.0	0.3
C2_F2_Peel	FLEX SOFT	0.146	0.375	0.185	0.217	0.425	0.338	0.361	0.329	0.190	0.797	0.3	0.2

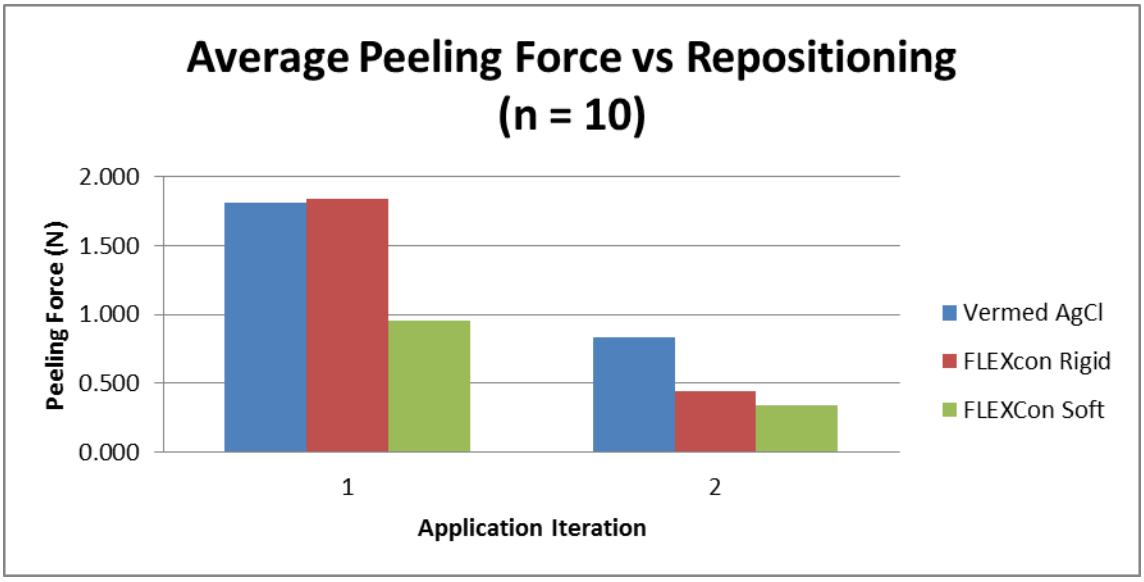


Figure 14: Average maximum peeling force required to remove each electrode type.

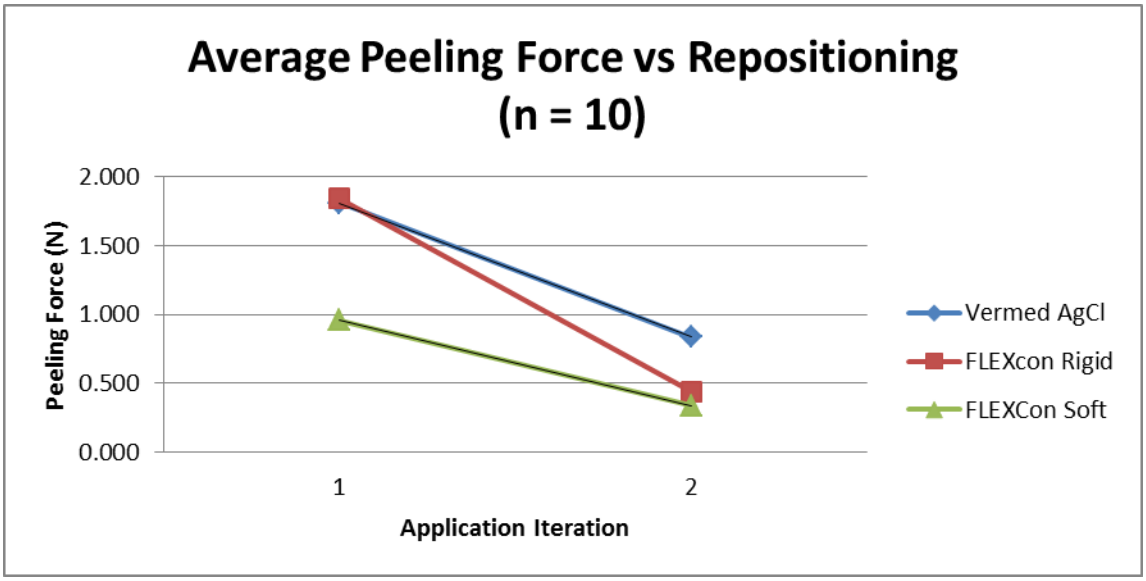


Figure 15: Comparison of adhesiveness losses between AgCl and FLEXcon electrodes (in response to peeling forces).

5.3 Phase I: Biocompatibility Experiment Results

The data were collected every day between 10 am and 12pm. The 10 subjects visited the laboratory every 24 hours for 15 minutes. After each subject answered the survey that asked about sensational irritation (itchiness and pain), pictures were taken of his or her arms for further analysis. The first three types of FLEXcon electrodes (Gen. 1, Gen. 2, and Gen. 2-A) were placed on the left forearm; the Gen. 3 and Ag/AgCl electrodes were placed on the right forearm. Figure 16 below shows the locations of all 5 types of electrodes placed on forearms.

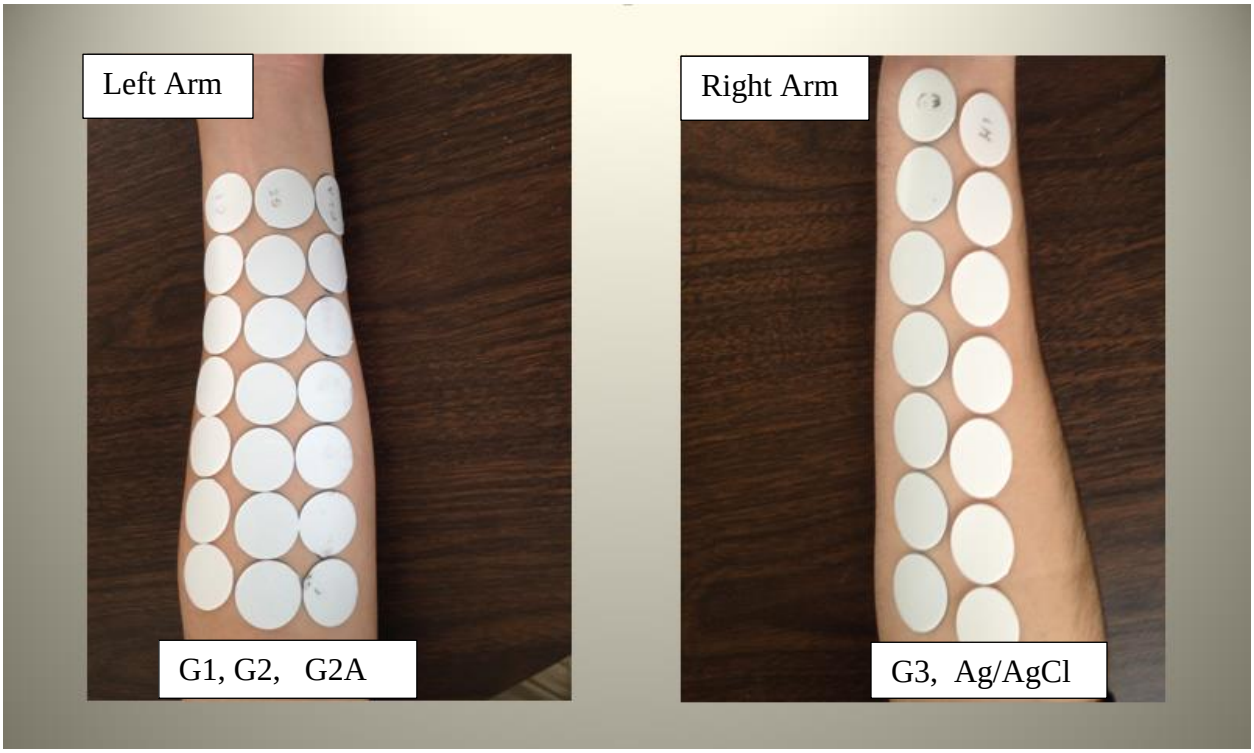


Figure 16: Day 1 placement of each type of electrode; G1, G2, G2-A, G3, and Ag/AgCl inside the forearm.

Pictures were taken with an iPhone5 (Apple, Inc.), which had 10 megapixel resolution, for observation of changes in skin coloration. The Figure 16 above shows electrode positioning immediately after the start of the clinical study. Figures 17-29 show the changes in skin

pigmentation throughout the progression of the 7-day clinical study. The Gen. 1 and Gen. 2 adhesives caused significant skin discoloration after wearing the electrodes for 72 hours, indicating that the salt concentrations in both adhesive types created a high osmolalic gradient that drew moisture from the skin. In response to the loss of water, there was significant skin inflammation. Throughout the 7-day procedure, the Gen. 3 adhesive had caused little to no skin irritation and inflammation; however, the composition of the electrode adhesive had exhibited high fall-off rates and weak electrode-to-skin adhesion. Although the Gen. 2-A adhesive left a dry, black carbon residue after removal from each subject's skin every day, slight changes in skin pigmentation were observed on the forearms of subjects 1 and 2, after 96 hours of experimentation. Periodic removal of the hydrogel electrodes showed no skin discoloration but left a clear wet residue.

Figure 17: Day 2 of the testing, subjects #1 thru #10 are shown with minor irritation to the skin.

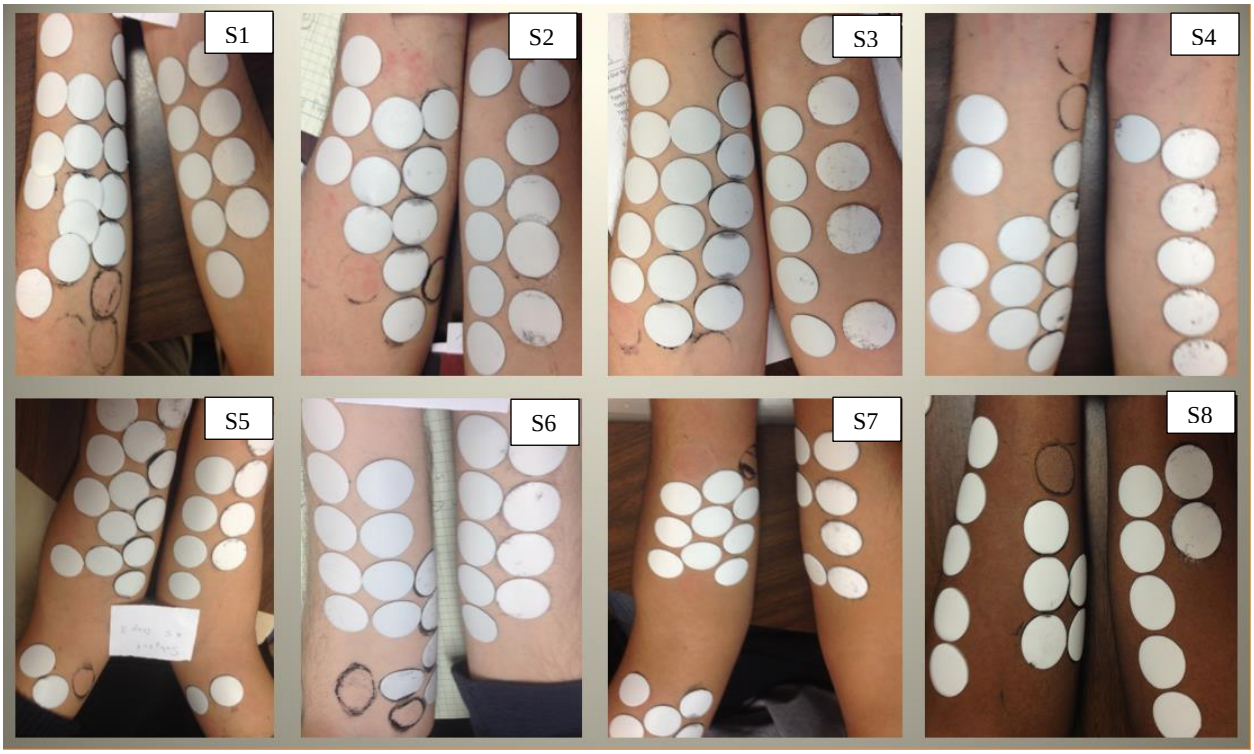


Figure 18: Day 3 of the study, Subjects #1 through #8 also no signs of irritation.

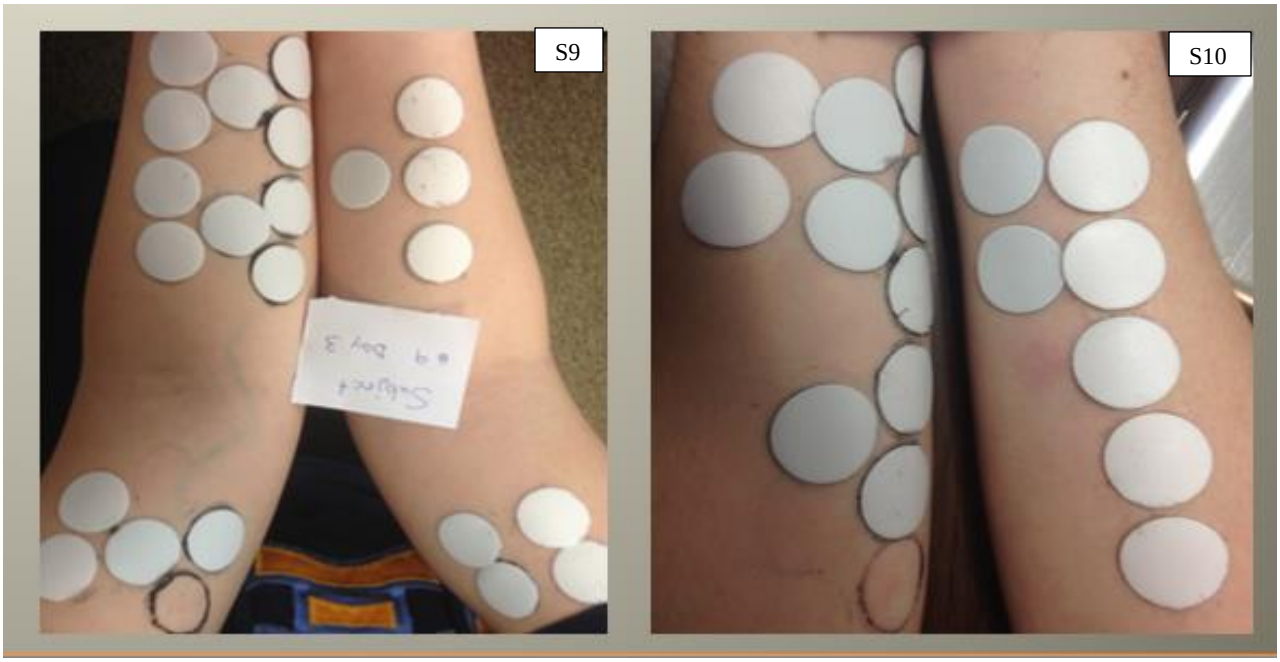


Figure 19: Day 3 of the study, Subjects #9 and #10 also no signs of irritation.

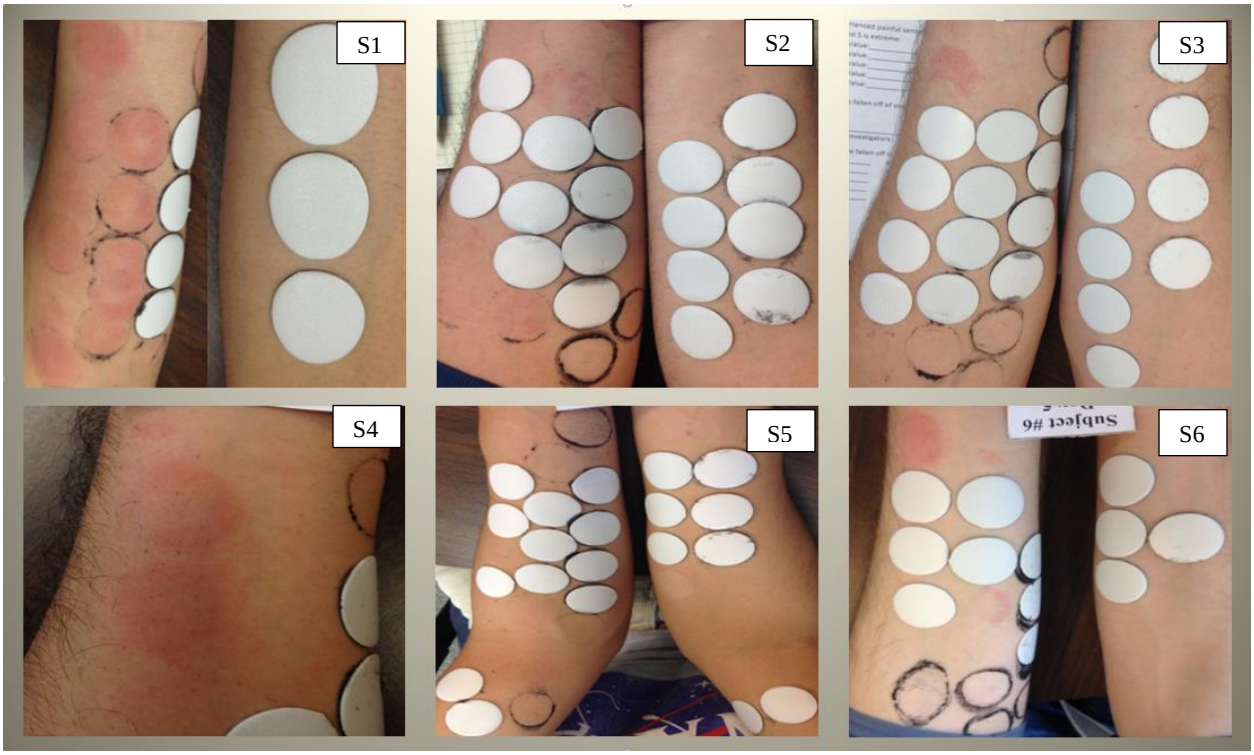


Figure 20: Day 4 of the study, Subjects #1 through #6 are showing irritation on the skin.

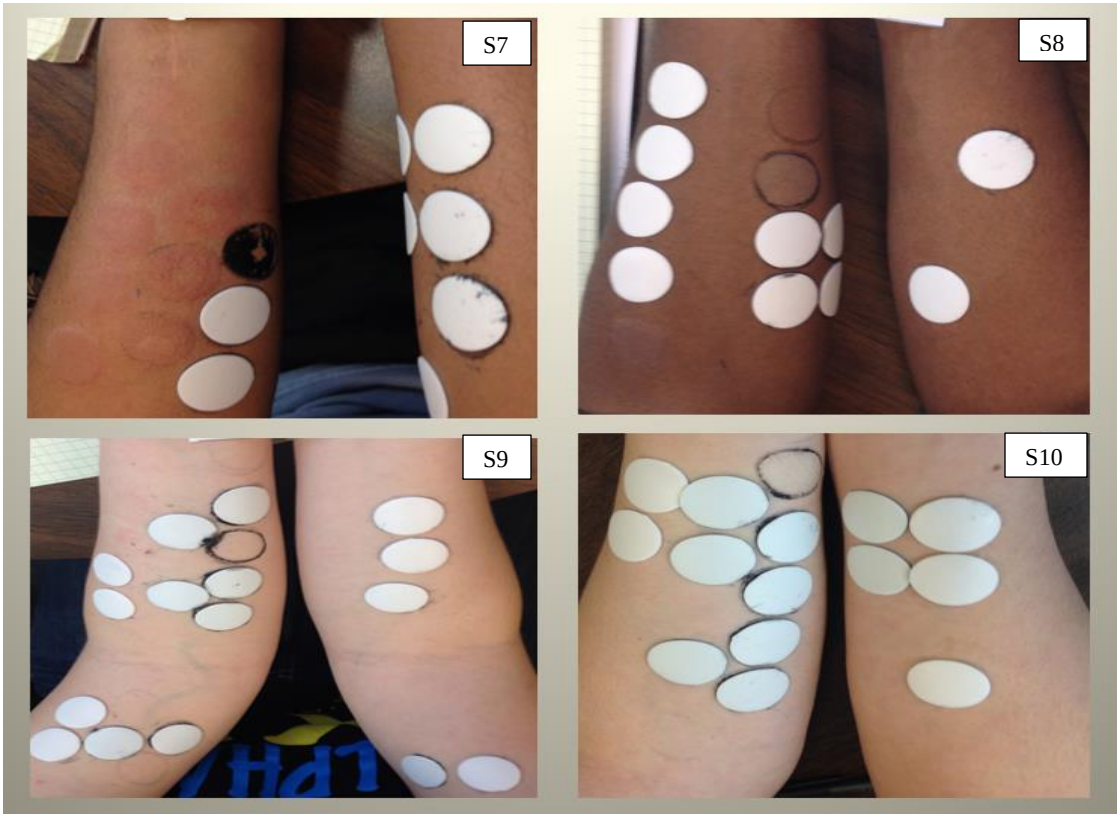


Figure 21: Day 4 of the study, Subjects #7 through #10 are also showing signs of skin irritation on the skin.

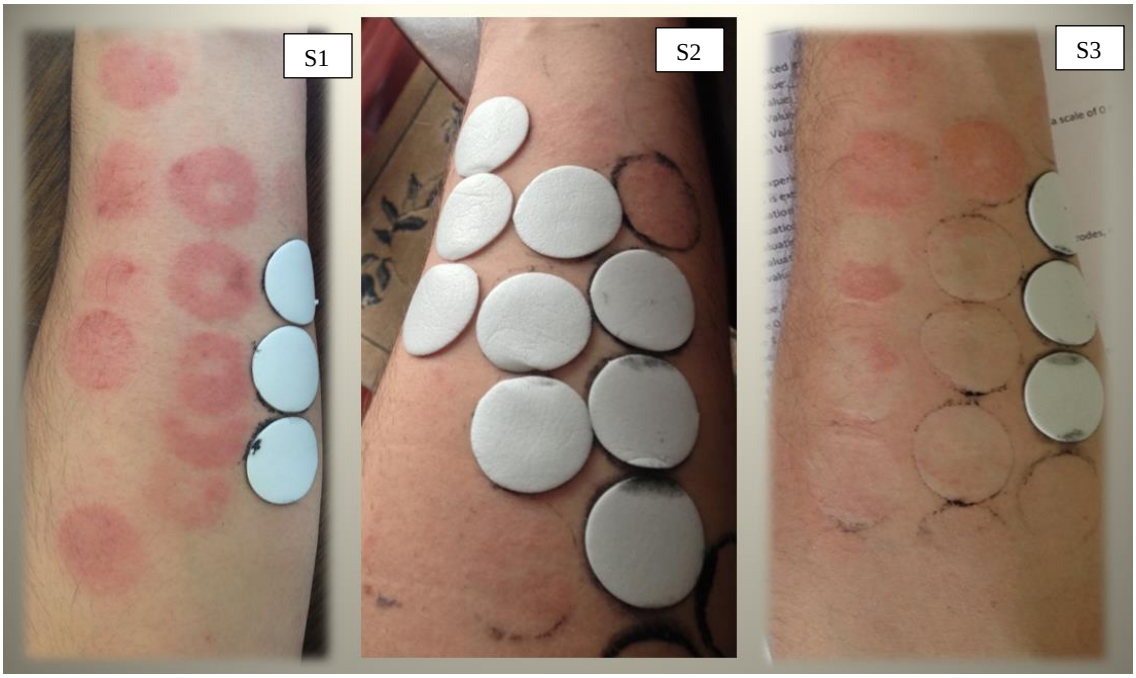


Figure 22: Day 5 of the study, Subjects #1 through #3 left arm skin irritation.

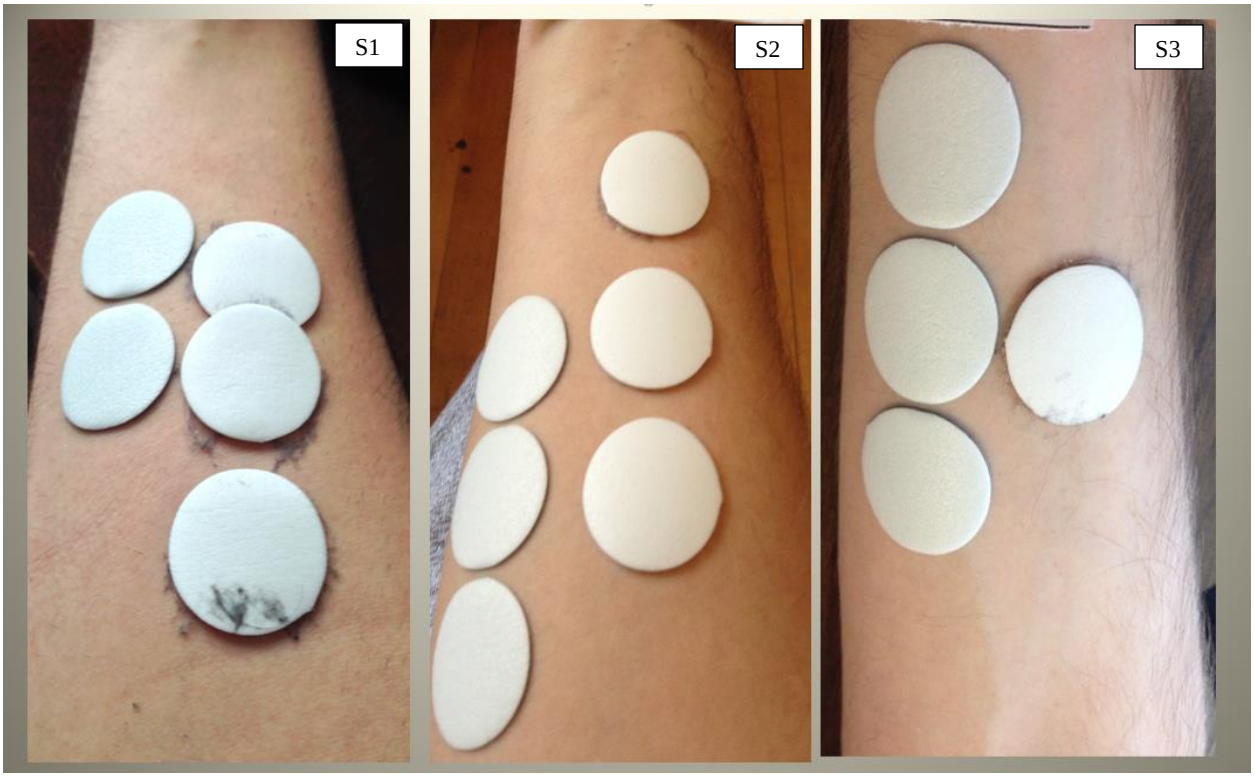


Figure 23: Day 5 of the study, Subjects #1 through #3 right arm no signs of skin irritation.

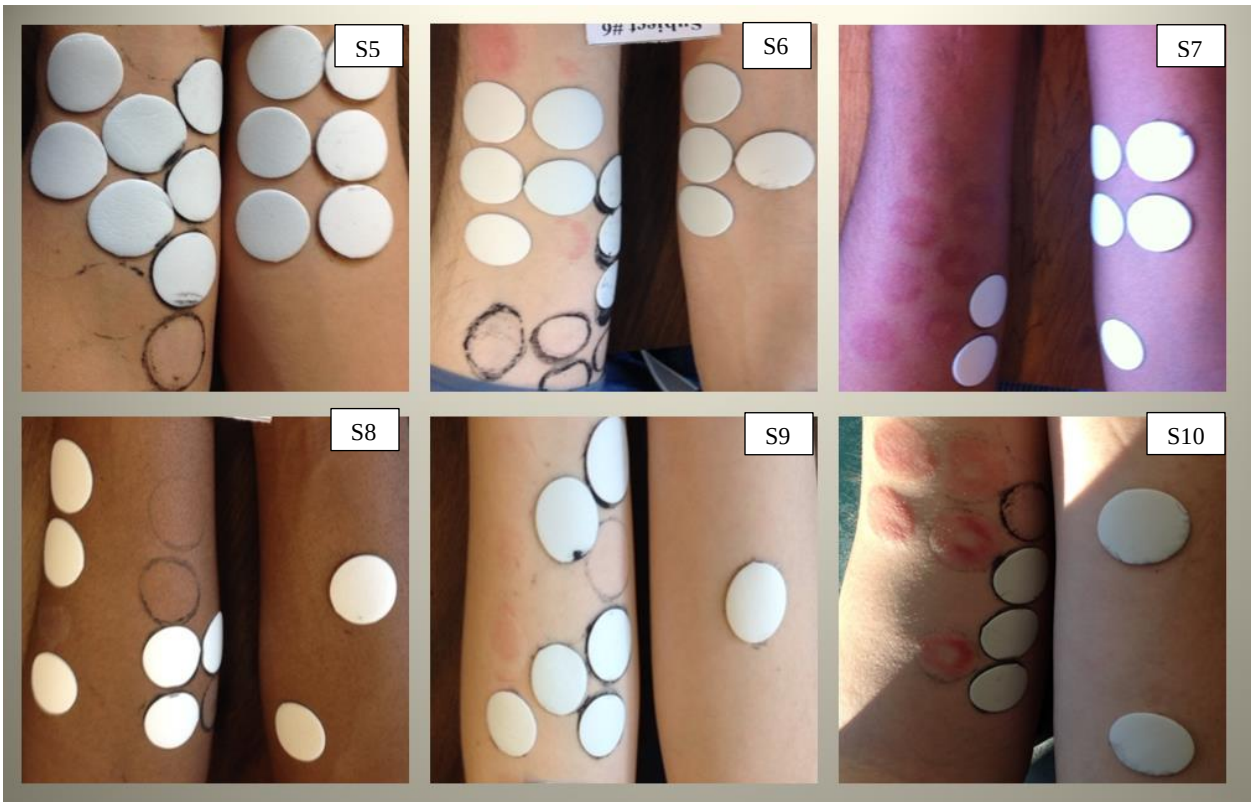


Figure 24: Day 5 Subjects #5 through #10.

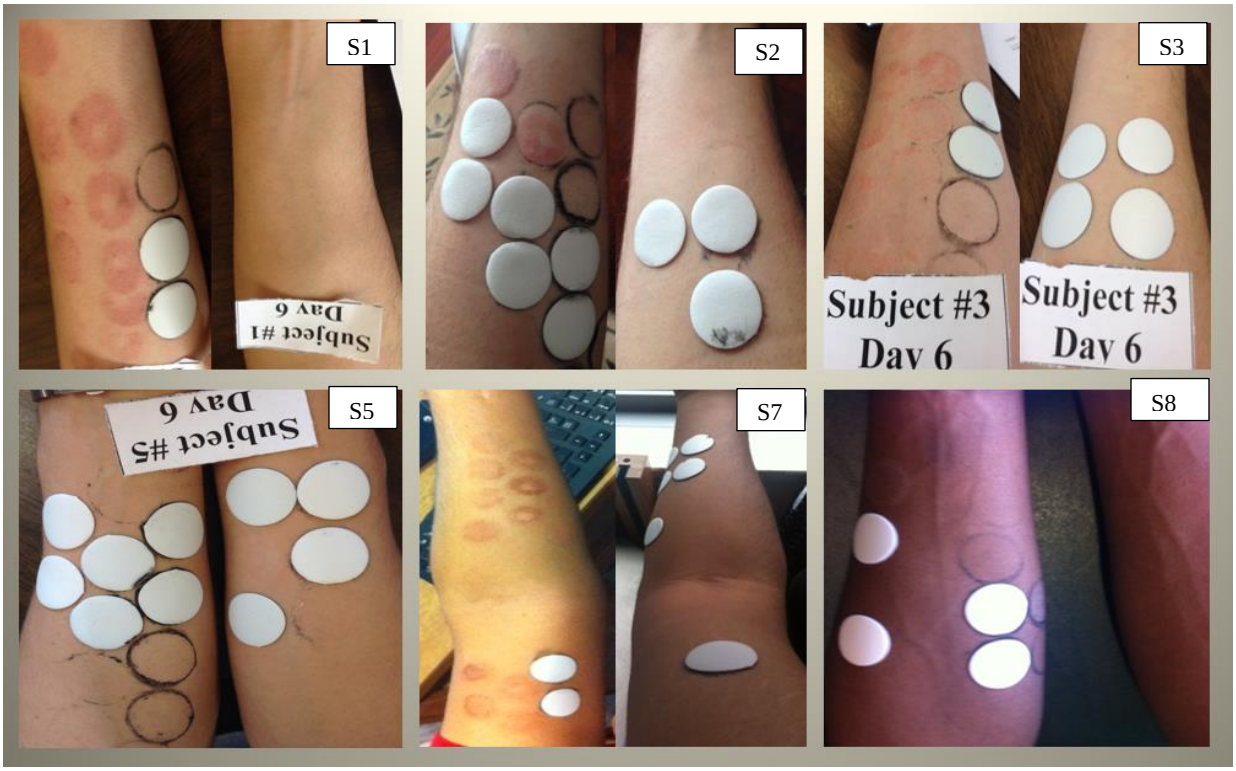


Figure 25: Day 6 Subject #1 through #8.

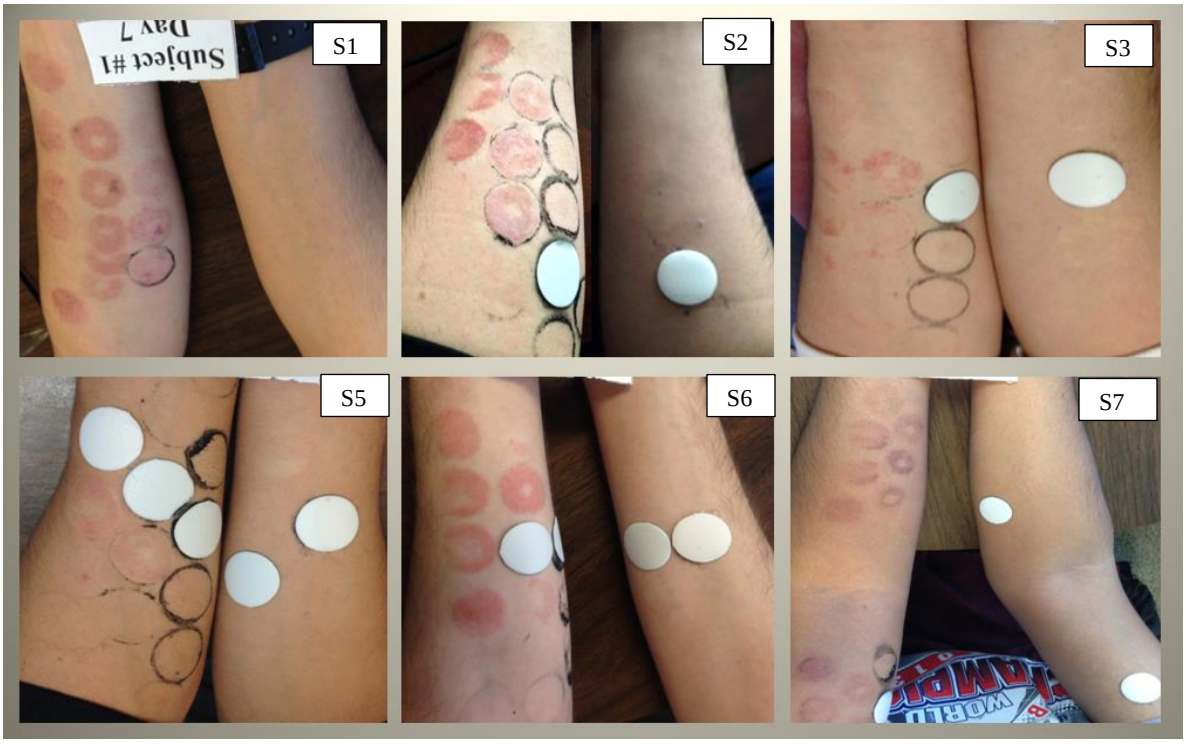


Figure 26: Day 7 Subject #1 through #7.

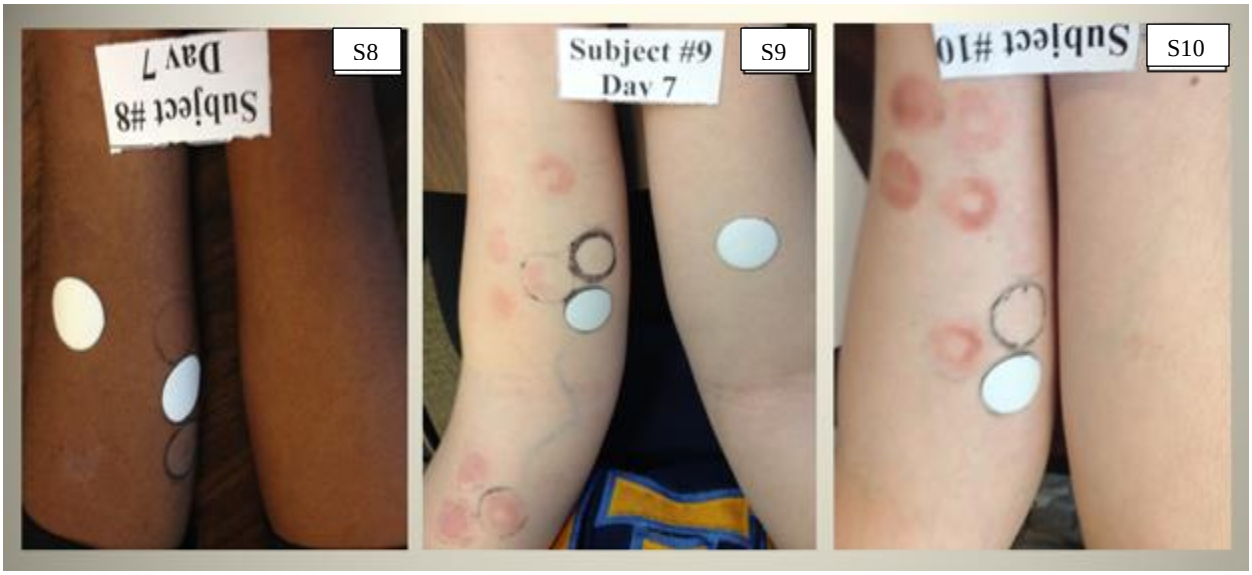


Figure 27: Day 7 Subject #8 through #10.

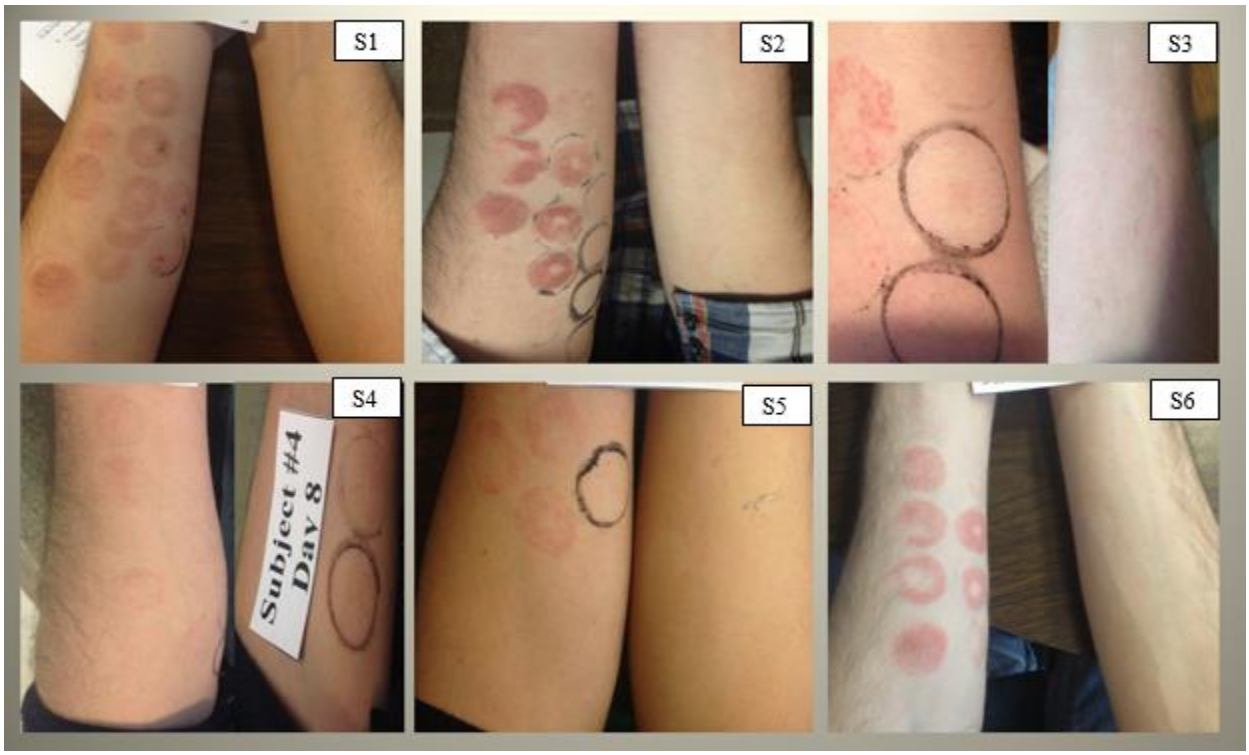


Figure 28: Day 8 Subjects #1 through #6.

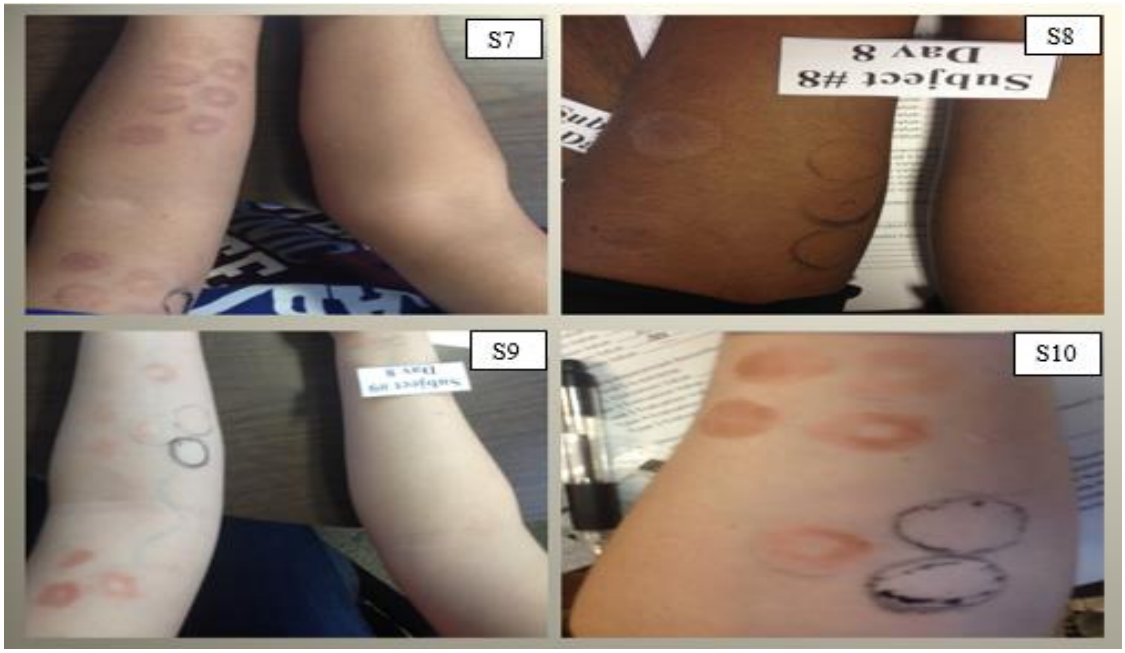


Figure 29: Day 8 Subjects #7 through #10.

5.4 Phase II: Short-Term Temperature Storage

One of the FLEXcon requirements was to measure and compare the integrity of the signal for FLEXcon's electrode to the hydrogel electrode (Ag/AgCl) under two extreme storage conditions. The two storage conditions that were chosen by FLEXcon were: 160 degrees Fahrenheit (F) and -80F. Another requirement was the measurement of the ECG with Ag/AgCl and FLEXcon electrodes after repositioning. The electrodes to be repositioned were stored at room temperature. The two ECG signals measured the FLEXcon and hydrogel electrodes were compared to determine the effect of extreme conditions on electrode performance.

The electrodes were placed for 72 hours at 160^{o}F and -80^{o}F before testing. The group selected ten participants to participate in the study. Each individual was schedule a time to visit the laboratory. After the arrival of each subject, he or she was asked to be seated in order for the team to conduct skin preparation prior to the placement of electrodes. The heart rate monitoring was performed while each subject was seated in a resting position. The equipment used for ECG signal acquisition was a BIOPAC System (BIOPAC Systems, Inc., Model MP100), as shown in Figure 30. The AcqKnowledge 3.9.1 software was then used for the capture and analysis of ECGs measured by the Ag/AgCl and FLEXcon electrodes.

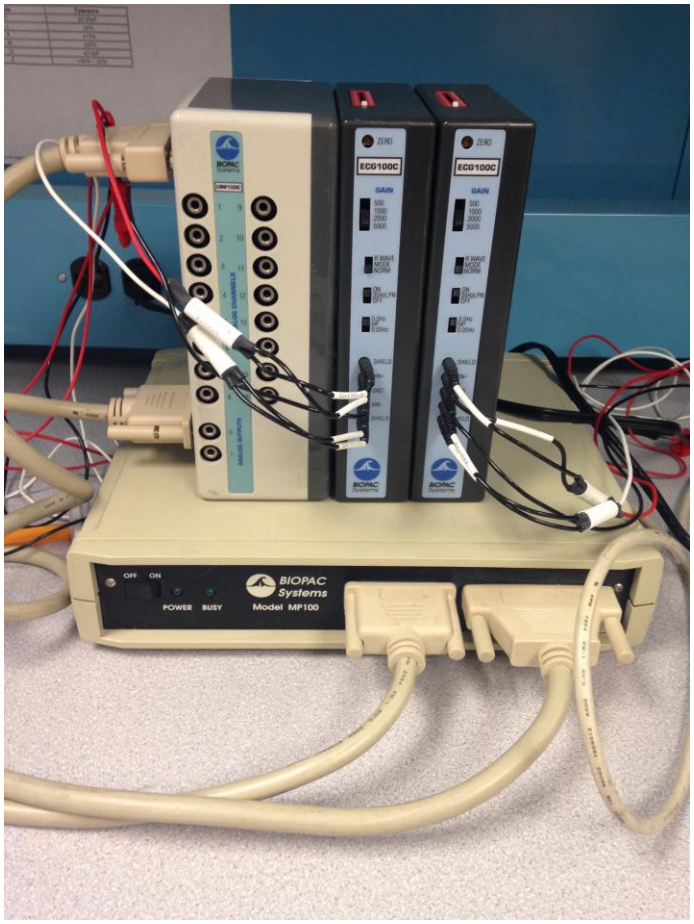


Figure 30: BIOPAC Systems the team used for short term signal processing under temperature storage conditions.

5.5 Phase II: Long-Term Stationary Results

The long term period was decided based on the results of the biocompatibility experiment. Because irritation was evident after 4 days, a testing period of 96 hours was selected. The ECG of each subject was measured during the morning and evening hours every day. Each visitation was 15 minutes. The first data set was collected in morning between 9 am to 12:30 pm for all 10 subjects. The second data set collected was in evening between 5 pm and 9 pm. ECG data were collected for 15 minutes for each time in morning and evening. The ECG data were collected in three stages. First, subjects were asked to sit in a seat for 5 minutes and remove all electronic devices. Next, subjects were asked to walk around the facility for 5 minutes to analyze

the capability of electrodes to detect changes in heart rate and reduce motion artifact interference. Then, the subjects returned to a stationary, resting position for the remaining 5 minutes. All data were uploaded subsequently to a computer and saved in a secure folder.

The skin preparation was done by removing shaving off any chest hair with a standard razor and dead skin with a standard ethyl alcohol pad. Skin preparation was done in order to maximize initial skin-to-electrode adhesion.

The five-lead electrode configuration was utilized to measure each subject's ECG. FLEXcon electrodes were placed next to Ag/AgCl electrodes for simultaneous, real-time comparison.

Table below shows the data calculated with MATLAB for day 1. The average of those data was calculated. The comparison of FLEXcon electrodes and Ag/AgCl electrodes, correlation coefficient was done based on table below for each of heart rate variability. All correlation of each data analysis were plotted on graphs with FLEXcon values on vertical axes and Ag/AgCl on horizontal axes. The slope of line that fit all the data shows the correlation coefficient, which means the percentage that those data are equal with each other.

Table 12: Heart Rate Variability (HRV) Analysis for Day 1

Subject #	fc_Found	fc_fixed	ag_found	ag_Fixed	LF_fc	LF_ag	HF_fc	HF_ag
1	194	1	194	0	8.57E+04	8.43E+04	6.76E+03	7.56E+03
2	166	1	166	0	1.57E+04	2.80E+04	1.75E+04	1.83E+04
3	180	0	180	0	4.15E+04	8.65E+03	8.76E+05	9.83E+03
4	190	4	190	0	3645100	3665800	104080	99705
5	140	0	140	0	7.45E+04	7.51E+04	4.09E+04	4.08E+04
6	176	2	176	0	2.04E+05	2.09E+05	7.78E+03	6.21E+03
7	175	0	175	0	3.39E+05	3.32E+05	2.77E+04	3.30E+04
8	148	0	148	0	5.16E+06	5.16E+06	3.06E+05	2.91E+05
9	174	0	174	0	5.06E+05	5.03E+05	3.00E+04	3.00E+04
10	146	0	146	0	1.18E+06	1.19E+06	7.83E+03	7.73E+03
				Average	1.13E+06	1.13E+06	1.42E+05	5.44E+04

Subject #	mean_bpm_f	mean_bpm_a	std_bpm_fc	std_bpm_ag	RMSSD_fc	RMSSD_ag	SDNN_fc	SDNN_ag
1	97.6225	97.8936	3.7941	5.1215	0.0134	0.0127	0.0242	0.0241
2	84.0144	83.5636	7.7474	4.8048	0.0246	0.0244	0.0416	0.0414
3	92.5277	91.1347	15.6057	10.5548	0.1405	0.0357	0.0877	0.03
4	95.8946	96.5097	7.2717	10.4417	0.0304	0.0303	0.0501	0.0494
5	70.6575	70.6433	5.4852	5.4482	0.055	0.055	0.0649	0.0649
6	89.2752	88.7258	8.0084	10.572	0.0228	0.0226	0.0416	0.0415
7	88.9117	89.1536	15.9128	18.9866	0.0283	0.0288	0.0476	0.0475
8	77.3088	77.1561	25.2158	23.509	0.076	0.0757	0.1038	0.1038
9	87.7624	87.7759	5.7345	5.7139	0.0253	0.025	0.0454	0.0452
10	74.3527	74.0289	7.4636	6.737	0.0383	0.0382	0.0731	0.0732
Average	85.83275	85.65852	10.22392	10.18895	0.04546	0.03484	0.058	0.0521

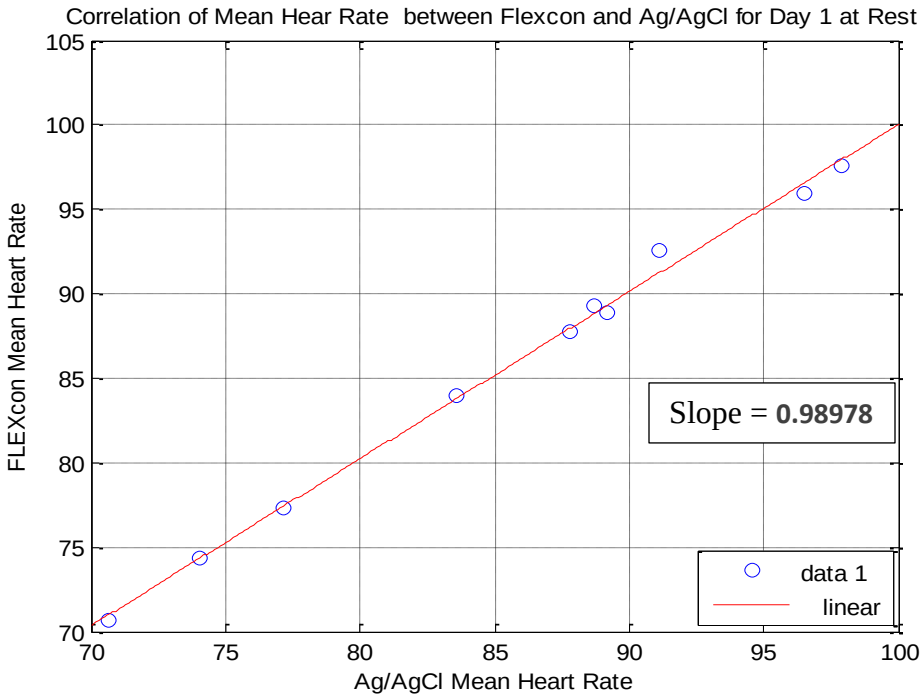


Figure 31: Correlation of Mean Heart Rate for FLEXcon and Ag/AgCl Day 1.

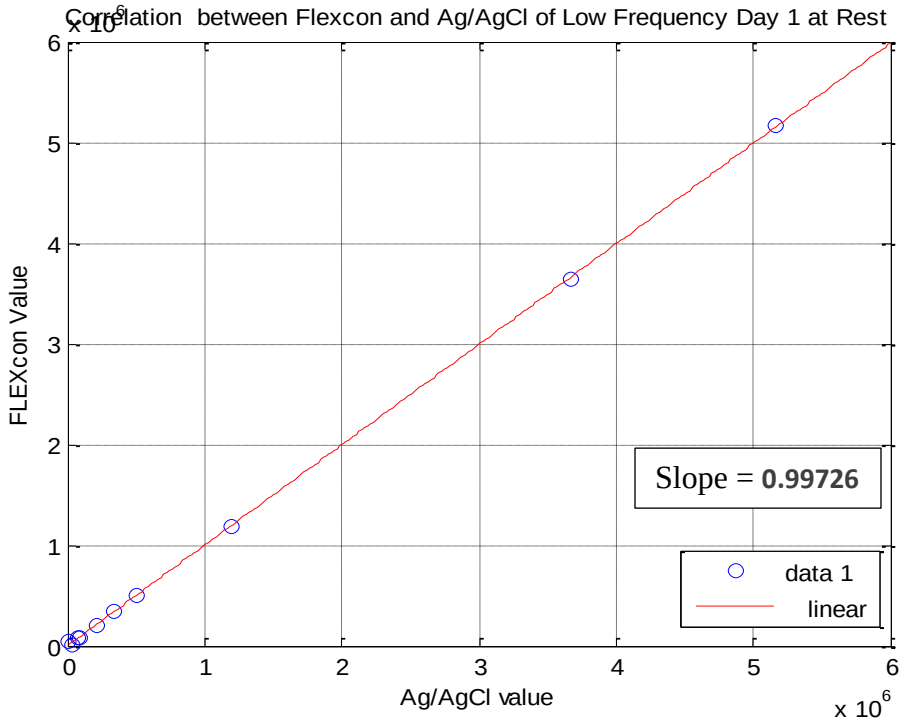


Figure 32: Correlation of Low Frequency for FLEXcon and Ag/AgCl, Day 1.

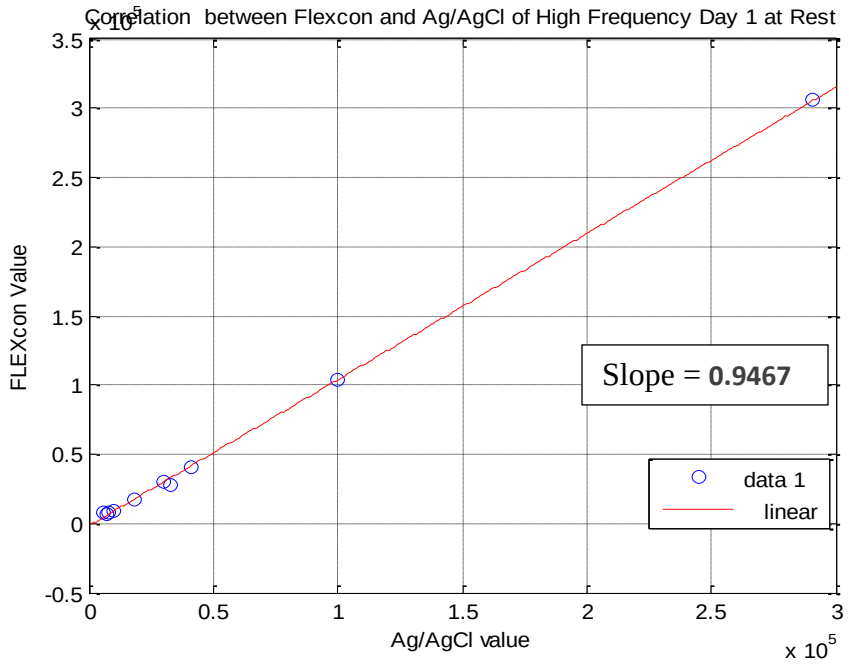


Figure 33: Correlation of High Frequency for FLEXcon and Ag/AgCl Day 1.

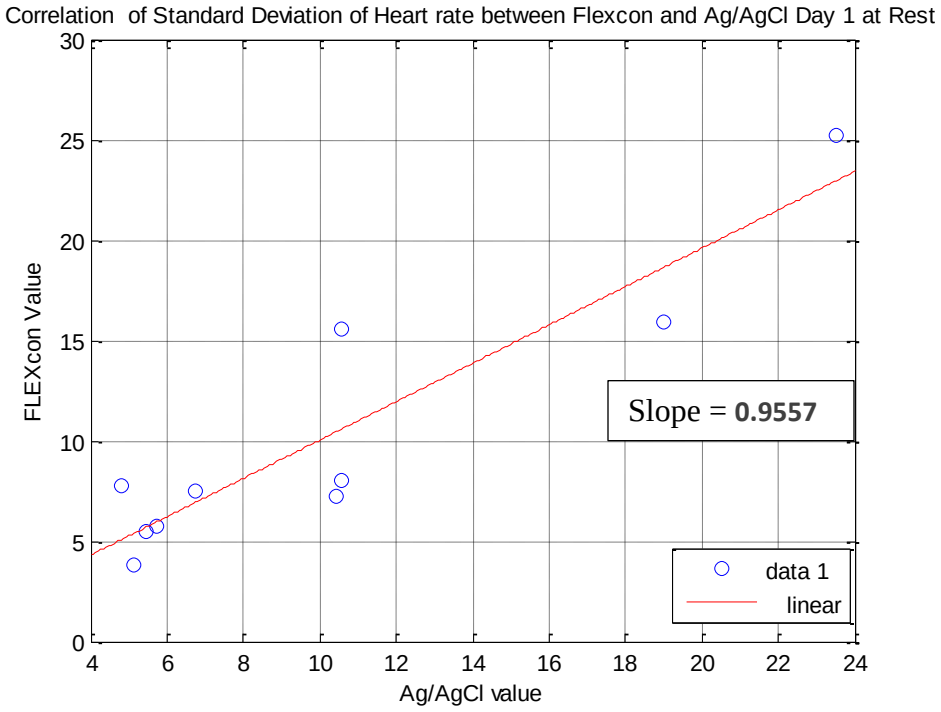


Figure 34: Correlation of STD of Mean Heart Rate for FLEXcon and Ag/AgCl Day 1.

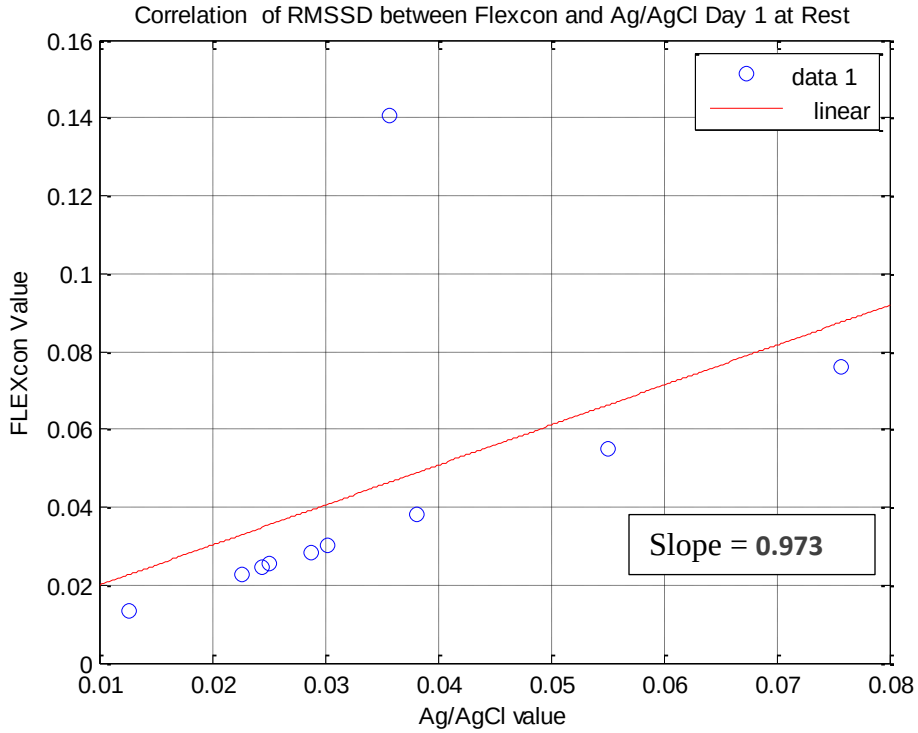


Figure 35: Correlation of RMSSD for FLEXcon and Ag/AgCl Day 1.

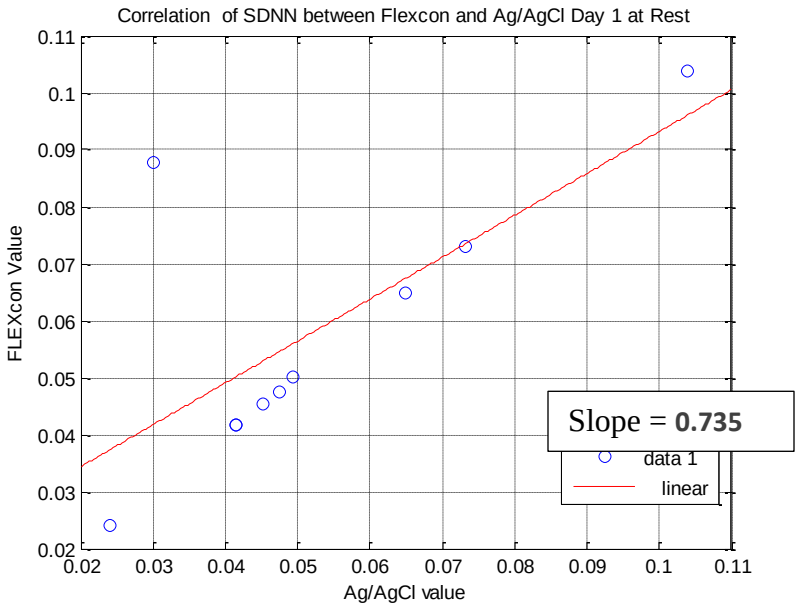


Figure 36: Correlation of SDNN for FLEXcon and Ag/AgCl Day 1.

The second day of the long term of the experiment most of the electrodes still adhered to the subjects' skin after each subject had taken a shower. Table 13 below shows all data measured on day 2 after analysis of heart rate variability. In order to compare both types of electrodes, the average of all heart rate measurements and the correlation coefficient (FLEXcon on vertical axes, Ag/AgCl on horizontal axes) for each metric were calculated. The correlation coefficient is the slope that both types of electrodes.

Table 13: HRV Analysis for Day 2.

Subject #	fc_Found	fc_fixed	ag_found	ag_Fixed	LF_fc	LF_ag	HF_fc	HF_ag
1	180	0	180	0	1.56E+06	1.57E+06	1.86E+04	1.90E+04
2	162	0	162	0	3.39E+06	3.46E+06	1.80E+04	1.52E+04
3	142	0	142	0	4.19E+04	3.92E+04	1.94E+04	2.01E+04
4	188	7	188	1	5.79E+05	5.73E+05	2.80E+05	2.51E+05
5	147	1	147	0	6.49E+05	6.41E+05	3.32E+04	3.49E+04
6	161	0	161	0	1.05E+05	1.05E+05	3.78E+03	3.56E+03
7	174	0	174	0	4.14E+05	4.27E+05	1.07E+04	1.07E+04
8	149	0	149	0	1.32E+06	1.28E+06	8.13E+04	8.56E+04
9	167	0	167	0	3.10E+05	3.18E+05	6.98E+03	7.25E+03
10	171	0	171	0	1.06E+07	1.01E+07	1.69E+05	1.49E+05
				Average	1.89E+06	1.85E+06	6.40E+04	5.96E+04
Subject #	mean_bpm_f	mean_bpm_a	std_bpm_fc	std_bpm_ag	RMSSD_fc	RMSSD_ag	SDNN_fc	SDNN_ag
1	92.6201	92.7259	28.8701	30.4293	0.0207	0.0209	0.0433	0.0433
2	83.5677	83.3017	27.0255	22.8211	0.0279	0.0281	0.0605	0.0605
3	71.7702	71.3252	5.7142	3.316	0.031	0.0322	0.04	0.0379
4	96.2296	95.0922	15.415	10.2059	0.0227	0.022	0.0642	0.0633
5	74.4689	74.6585	7.018	7.8959	0.0516	0.0517	0.074	0.074
6	82.8913	82.7336	24.7182	22.7581	0.0268	0.027	0.0533	0.0535
7	87.5594	87.9317	5.9443	7.2144	0.0247	0.0249	0.0472	0.0473
8	75.4804	75.4513	7.7833	7.7419	0.0443	0.0438	0.0833	0.0831
9	84.248	84.2753	4.8402	4.9214	0.0196	0.0196	0.0404	0.0405
10	86.6588	86.8524	8.3679	8.6896	0.0503	0.0504	0.0737	0.0738
Average	83.54944	83.43478	13.56967	12.59936	0.03196	0.03206	0.05799	0.05772

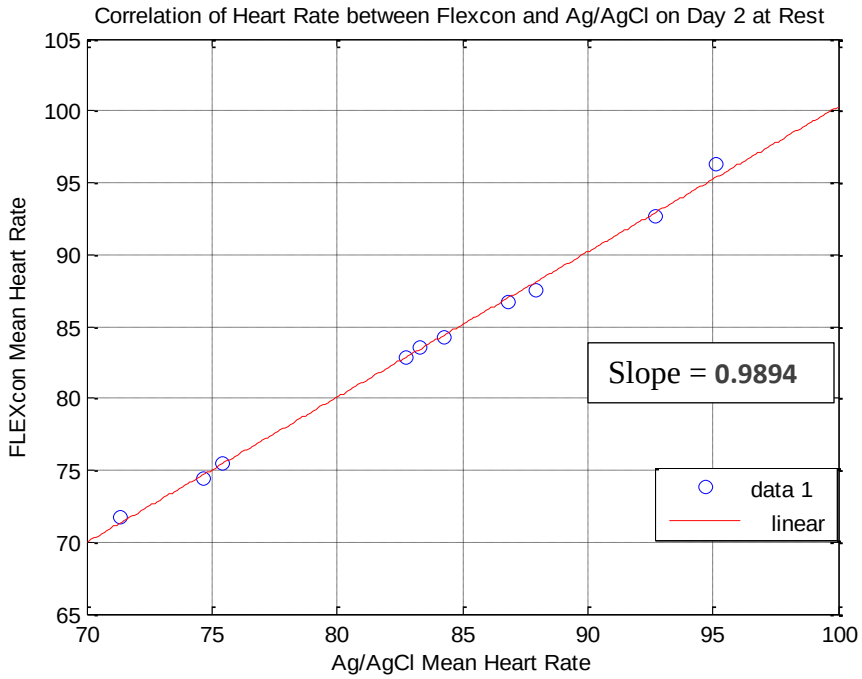


Figure 37: Correlation of Mean Heart Rate for FLEXcon and Ag/AgCl Day 2.

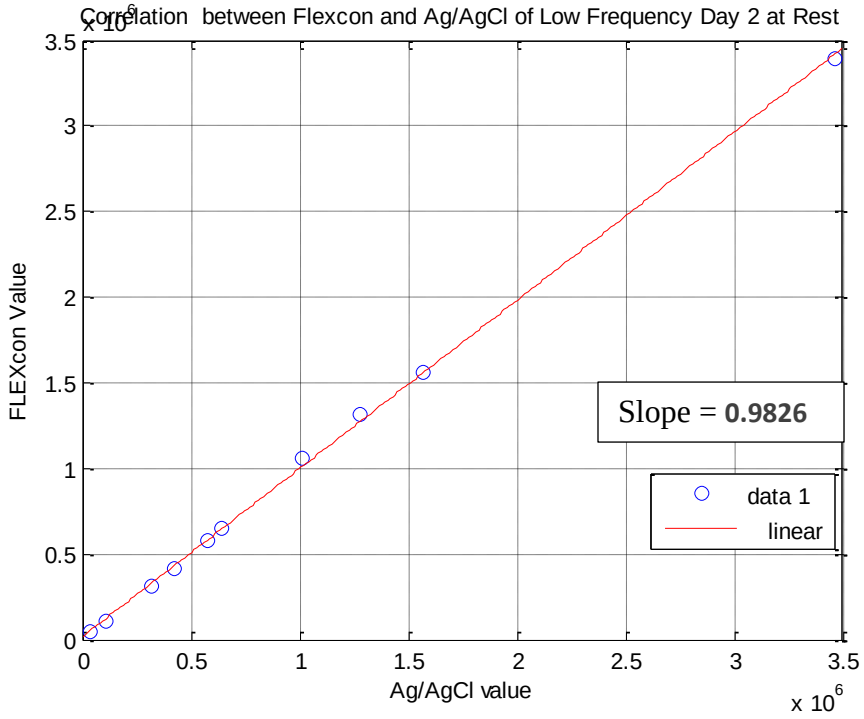


Figure 38: Correlation of Low Frequency for FLEXcon and Ag/AgCl, Day 2.

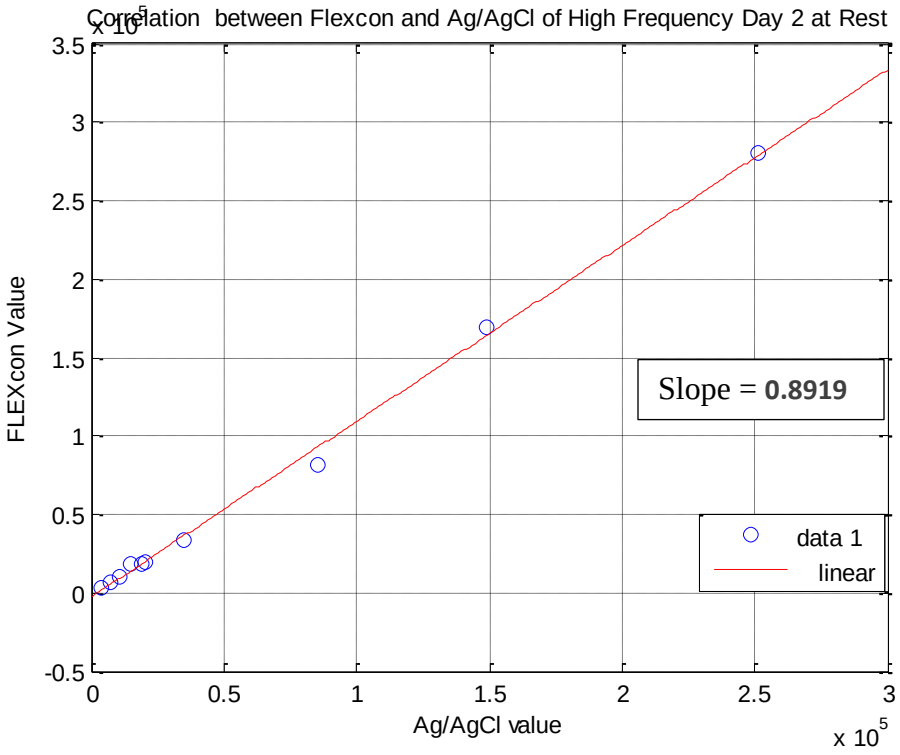


Figure 39: Correlation of High Frequency for FLEXcon and Ag/AgCl Day 2.

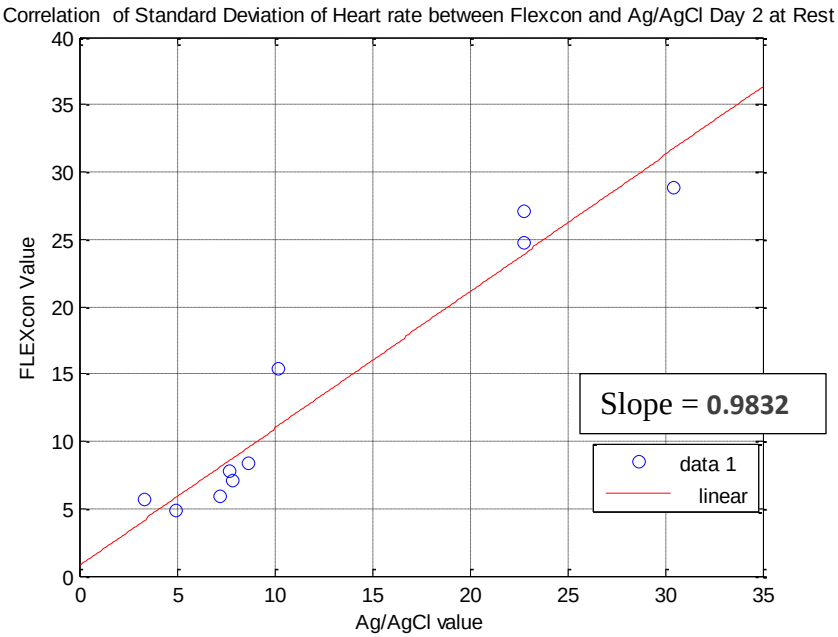


Figure 40: Correlation of STD of Mean Heart Rate for FLEXcon and Ag/AgCl Day 2.

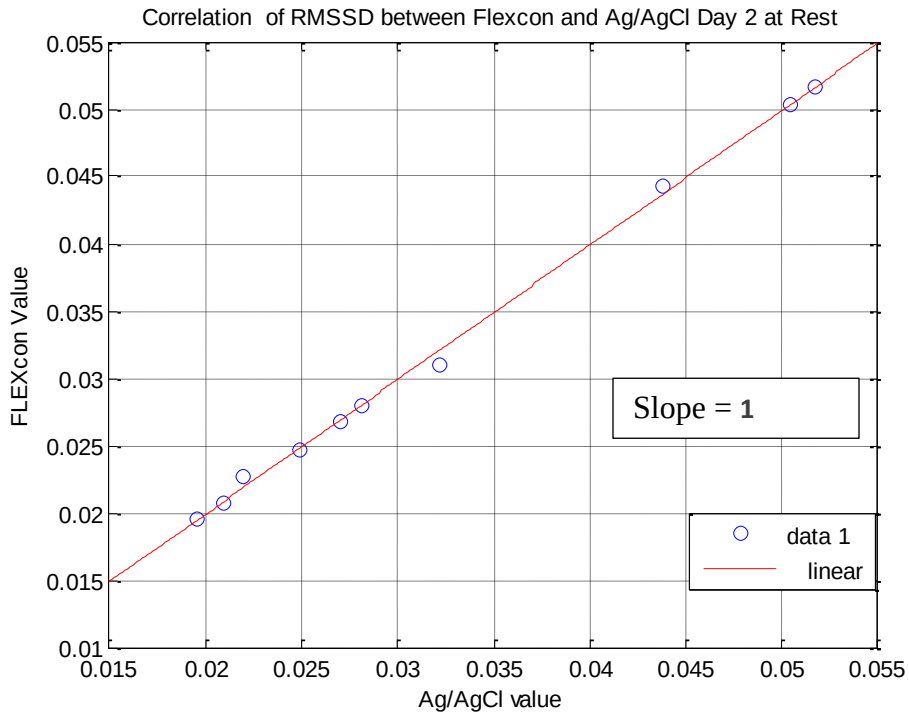


Figure 41: Correlation of RMSSD for FLEXcon and Ag/AgCl Day 2.

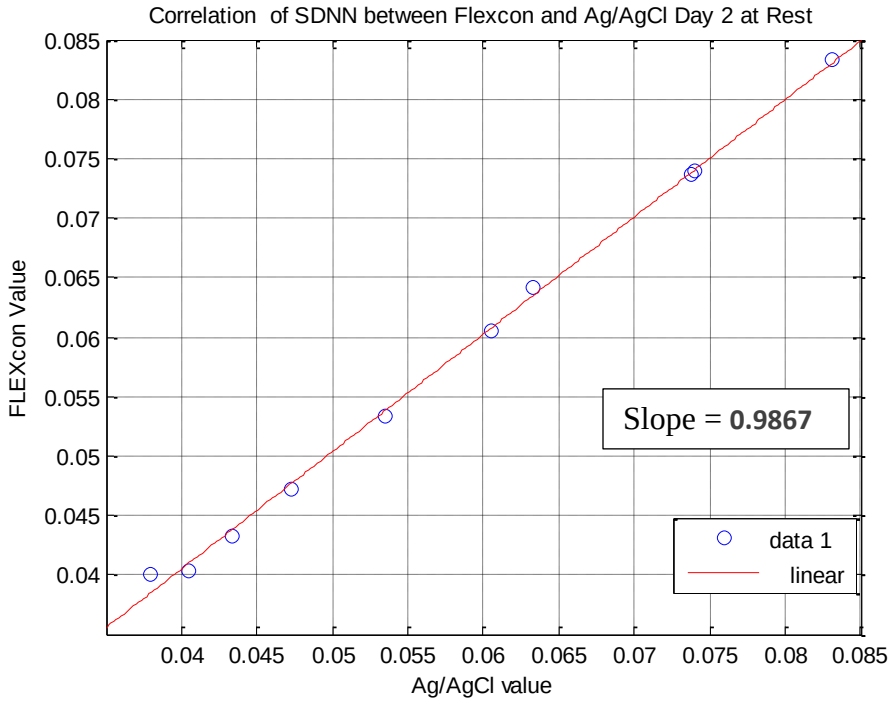


Figure 42: Correlation of SDNN for FLEXcon and Ag/AgCl Day 2.

All the data were collected for each subjects after the monitoring the skin and adhesion of both types of electrodes. Subject 1, 2, 3, 5, 7, 8, and 10 did not had any problem with electrodes fallen off and neither for skin iteration or itchiness. Subject 4 had extremely itchiness from all electrodes. All electrodes were reposition in order to reduce itchiness and for data recording. After, all electrodes were taped with adhesive with holes in order for the skin to breathe. Subject 6 had extremely itchy skin from all electrodes. All electrodes were reposition in order to allow irritated skin to breath. Subject 9 had unbearable skin iteration and all electrodes were reposition in order to allow the irritated skin to breath. After, all electrodes were taped in order to collect data. Table below shows all the data collected for heart rate variability measurements for analysis. The average was calculated and then the coefficient correlation graphs with their slope.

Table 14: HRV Analysis for Day 3.

Subject #	fc_Found	fc_fixed	ag_found	ag_Fixed	LF_fc	LF_ag	HF_fc	HF_ag
1	160	0	160	0	2.94E+05	3.18E+05	1.06E+04	1.07E+04
2	133	0	133	0	5.09E+04	4.85E+04	9.85E+04	9.54E+04
3	139	0	139	0	3.66E+11	5.71E+13	7.46E+13	2.33E+16
4	162	2	162	0	3.92E+05	4.10E+05	5.86E+03	6.31E+03
5	172	0	172	0	1.78E+06	1.80E+06	4.86E+04	4.66E+04
6	164	0	164	0	2.78E+05	2.76E+05	6.23E+03	6.79E+03
7	172	0	172	0	1.25E+06	1.27E+06	1.42E+04	1.46E+04
8	150	0	150	0	3.39E+06	3.27E+06	8.15E+04	8.67E+04
9	182	0	182	0	4.16E+05	4.35E+05	1.95E+04	1.60E+04
10	153	0	153	0	1.38E+05	1.37E+05	3.13E+03	2.57E+03
				Average	3.66E+10	5.71E+12	7.46E+12	2.33E+15

Subject #	mean_bpm_fc	mean_bpm_ag	std_bpm_fc	std_bpm_ag	RMSSD_fc	RMSSD_ag	SDNN_fc	SDNN_ag
1	80.5103	81.33	7.3191	7.2245	0.0242	0.0242	0.0416	0.0419
2	67.8233	67.3478	4.0869	4.3922	0.0589	0.0591	0.0584	0.0587
3	107.8288	108.7619	7.932	6.5501	0.1218	0.1092	0.0937	0.0909
4	81.7915	81.4805	6.9869	4.8585	0.0326	0.034	0.0441	0.0444
5	87.9018	87.9973	11.1031	11.1095	0.0421	0.0418	0.0899	0.0899
6	82.8127	82.9523	9.216	10.7078	0.0277	0.0275	0.0488	0.0488
7	87.6696	88.1649	12.1513	15.9898	0.0364	0.0359	0.0839	0.0836
8	76.1319	76.587	8.1209	11.8667	0.0436	0.0435	0.0707	0.0708
9	91.9618	91.6926	7.6614	5.3623	0.0218	0.0201	0.0382	0.0378
10	78.3901	78.3655	11.5837	11.4098	0.0326	0.0325	0.0966	0.0965
Average	84.28218	84.46798	8.61613	8.94712	0.04417	0.04278	0.06659	0.06633

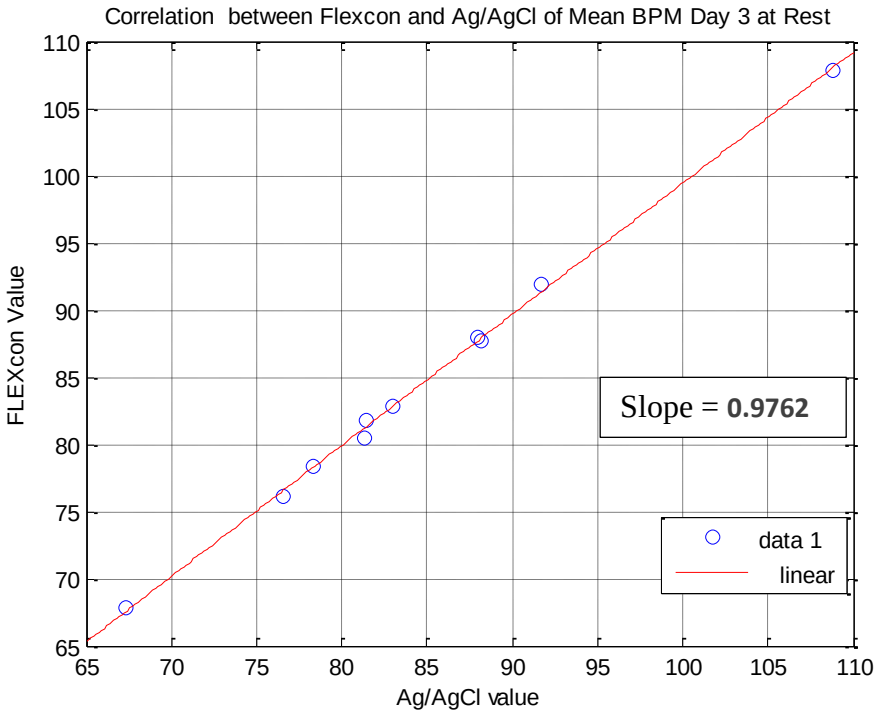


Figure 43: Correlation of Mean Heart Rate for FLEXcon and Ag/AgCl Day 3.

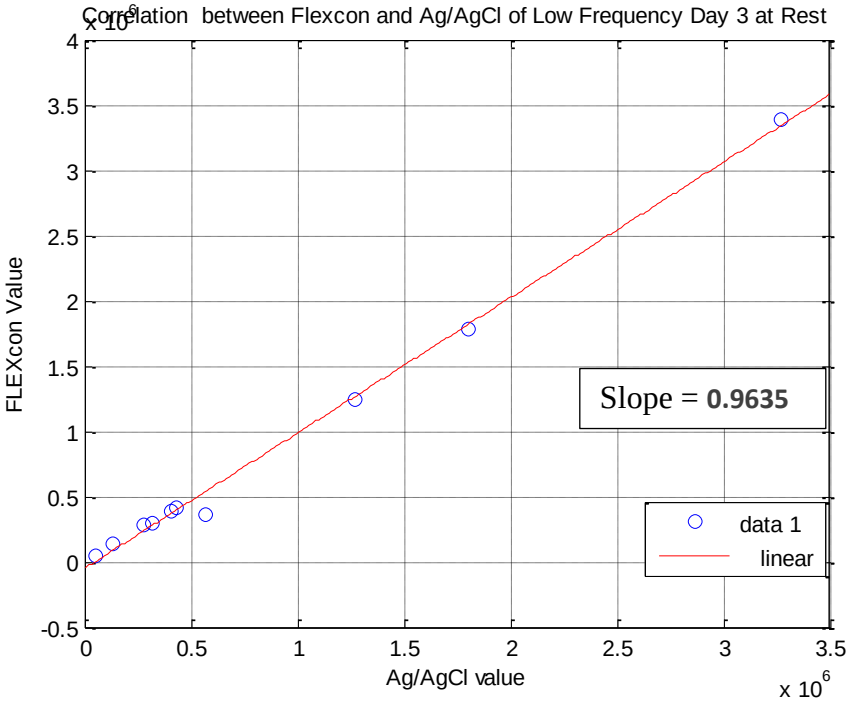


Figure 44: Correlation of Low Frequency for FLEXcon and Ag/AgCl, Day 3.

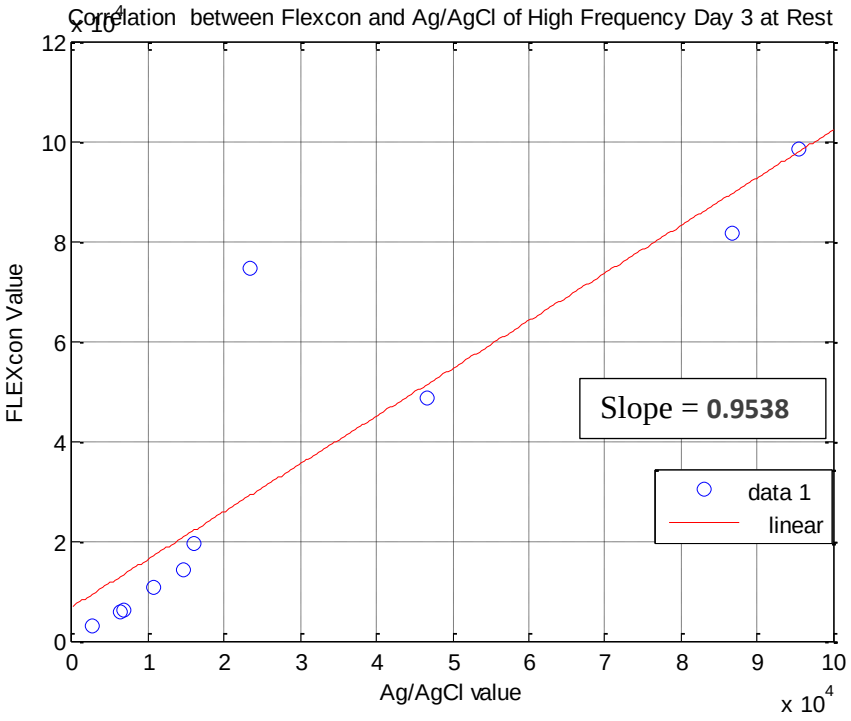


Figure 45: Correlation of High Frequency Signal Power for FLEXcon and Ag/AgCl Day 3.

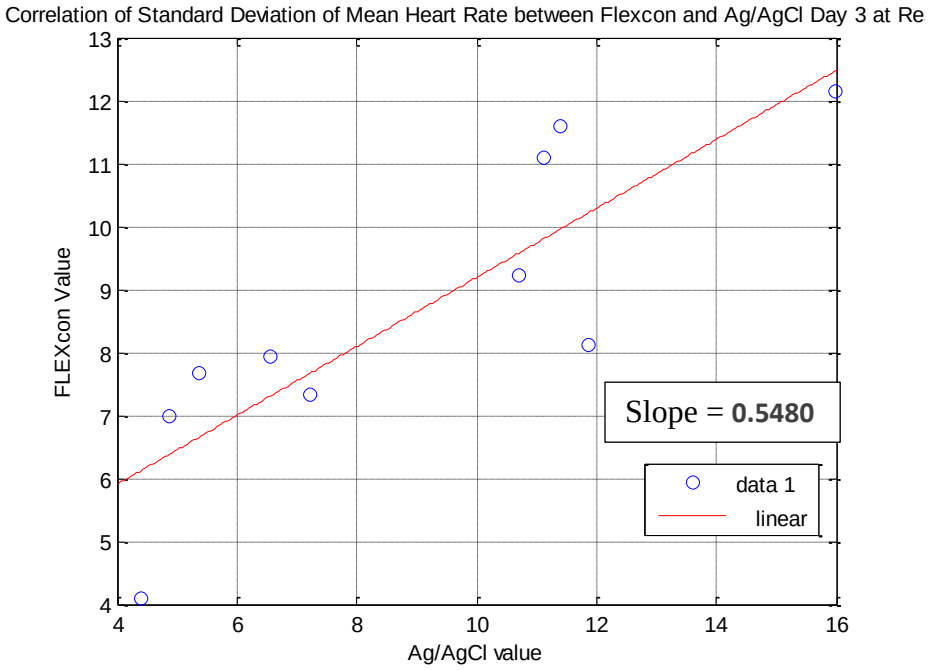


Figure 46: Correlation of STD of Mean Heart Rate for FLEXcon and Ag/AgCl Day 3.

As shown in Figure 46, there was a significant difference between the FLEXcon and hydrogel measurements of HRV. The value of the correlation coefficient (0.5480) shows that the variation of heart rate measured by the Ag/AgCl electrodes was approximately two times that measured by the FLEXcon electrodes. Because the subjects were in relaxed and resting positions during data acquisition, their heart rates were stable with average deviations of 8.62 (FLEXcon) and 8.94 (hydrogel) beats per minute (Table 14). This increase in measured heart rate standard deviation suggests that the precision of peak detection in the algorithm has decreased during calculations of R-R intervals in the Ag/AgCl ECG waveform. The indexing of peak locations on the QR or RS complexes, instead of the R wave itself, was the most likely cause of larger heart rate variances.

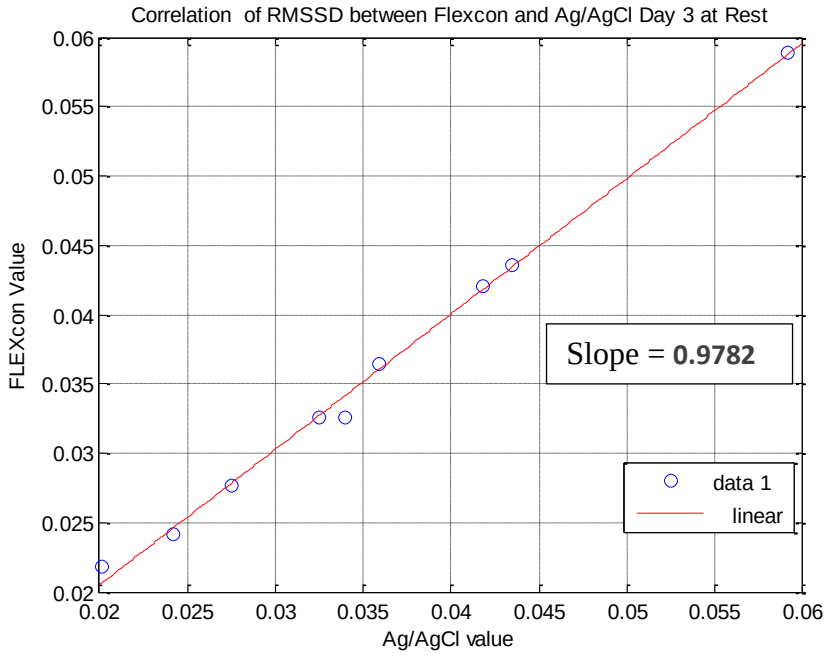


Figure 47: Correlation of RMSSD for FLEXcon and Ag/AgCl Day 3.

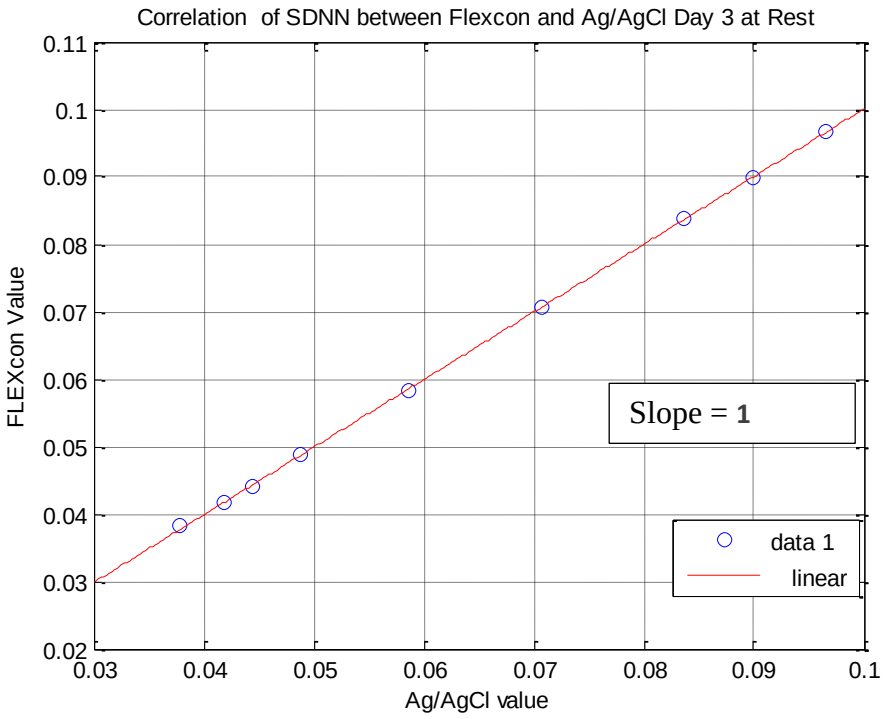


Figure 48: Correlation of SDNN for FLEXcon and Ag/AgCl, Day 3.

The day 4 of the experiment for long term stationary electrodes were taped for all 10 subjects in order to keep them on place for better data recording. Subject 4 had to reposition all electrodes because skin was burning and had sensations. After making sure all electrodes were on place and had good conduction with skin, data recording started for 15 minutes.

Table below shows all data measurements for day 4 or after 72 hours. Subject 10 was not placed on table below because the Ag/AgCl measurements were very bad and FLEXcon were good. In order to compare both data with similarities the entire data for subject 10 was removed and compare both types of electrodes with nine subjects. The average was calculated as it is shown on table below and correlation coefficient was done between FLEXcon electrodes and Ag/AgCl electrodes.

Table 15: HRV Analysis for Day 4.

Subject #	fc_Found	fc_fixed	ag_found	ag_Fixed	LF_fc	LF_ag	HF_fc	HF_ag
1	165	0	165	0	3.31E+05	3.29E+05	2.99E+04	2.98E+04
2	163	0	163	0	5.90E+05	6.84E+05	9.85E+03	2.01E+04
3	151	0	151	0	5.33E+04	4.12E+04	3.31E+05	1.17E+04
4	213	2	213	5	2.29E+06	2.18E+06	7.37E+04	6.55E+04
5	213	2	213	5	2.29E+06	2.18E+06	7.37E+04	6.55E+04
6	144	0	144	0	1.13E+05	1.13E+05	1.18E+04	1.09E+04
7	163	0	163	0	1.83E+06	1.82E+06	4.27E+04	4.20E+04
8	135	0	135	0	8.89E+05	8.89E+05	1.97E+05	2.00E+05
9	182	0	182	0	5.00E+05	5.06E+05	6.47E+03	6.14E+03
10								
				Average	9.87E+05	9.71E+05	8.62E+04	5.02E+04

Subject #	mean_bpm_fc	mean_bpm_ag	std_bpm_fc	std_bpm_ag	RMSSD_fc	RMSSD_ag	SDNN_fc	SDNN_ag
1	83.7658	83.6528	10.7085	9.5903	0.0313	0.0308	0.0545	0.0545
2	82.2916	84.3751	5.805	8.4912	0.0275	0.0272	0.0522	0.0522
3	77.9508	77.2174	6.919	7.901	0.0863	0.0445	0.0605	0.0431
4	107.5271	107.2472	10.0532	7.751	0.0172	0.0178	0.0411	0.0411
5	107.5271	107.2472	10.0532	7.751	0.0172	0.0178	0.0411	0.0411
6	73.2103	73.1188	11.255	10.3622	0.0428	0.0422	0.064	0.0639
7	82.7782	82.7461	9.4426	9.1954	0.0399	0.0388	0.0646	0.0644
8	68.7481	68.8141	8.1607	8.431	0.0719	0.0718	0.0989	0.099
9	91.882	91.8806	4.7078	4.693	0.0187	0.0184	0.0333	0.0332
10								
Average	86.1867778	86.2554778	8.56722222	8.24067778	0.0392	0.03436667	0.05668889	0.05472222

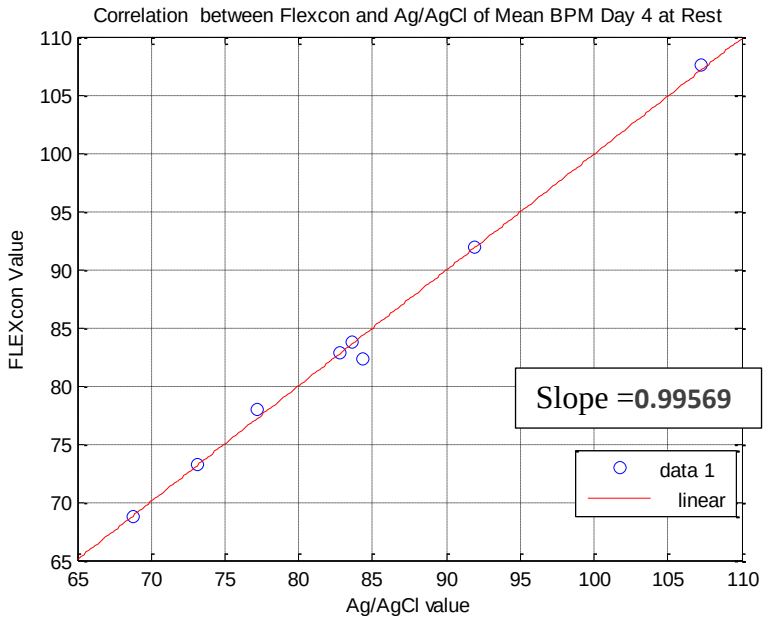


Figure 49: Correlation of Mean Heart Rate for FLEXcon and Ag/AgCl, Day 4.

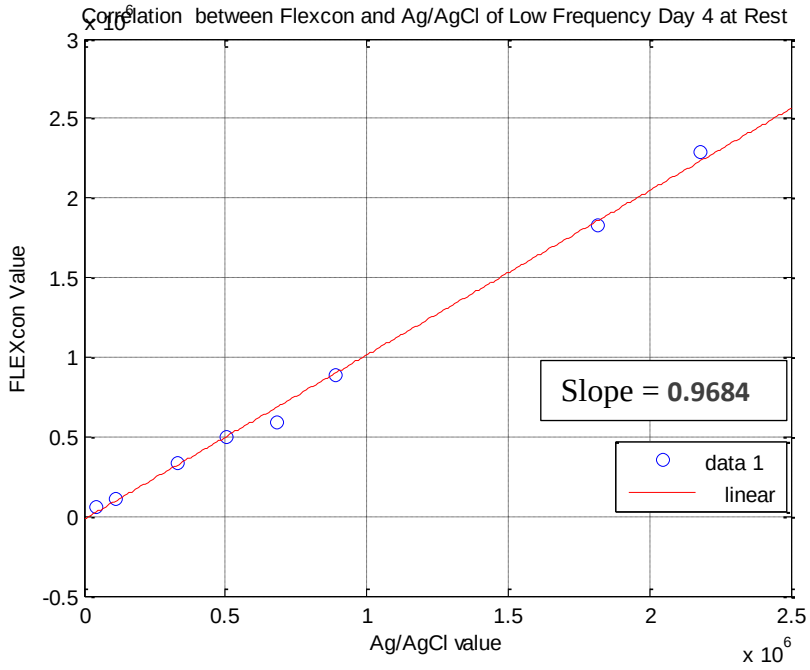


Figure 50: Correlation of Low Frequency for FLEXcon and Ag/AgCl, Day 4.

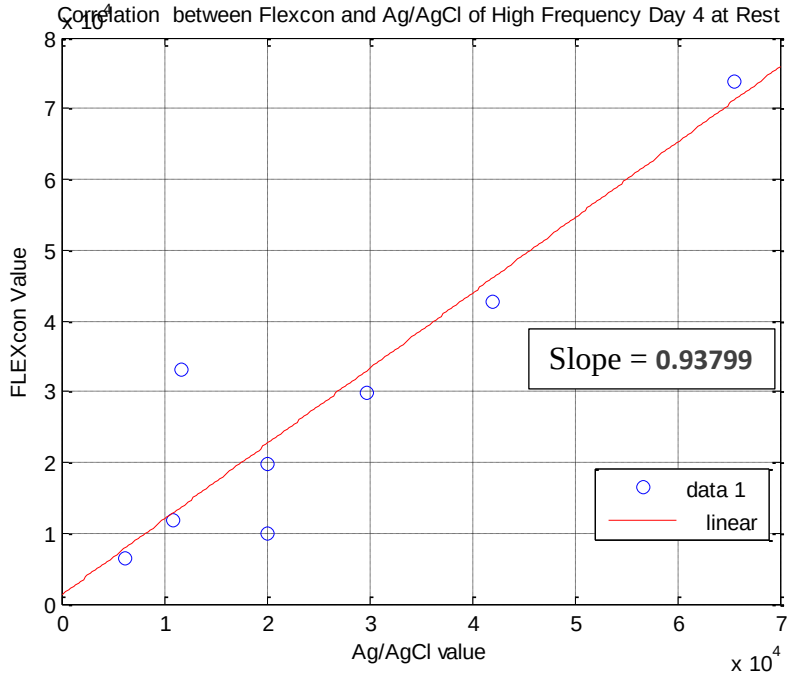


Figure 51: Correlation of High Frequency for FLEXcon and Ag/AgCl Day 4.

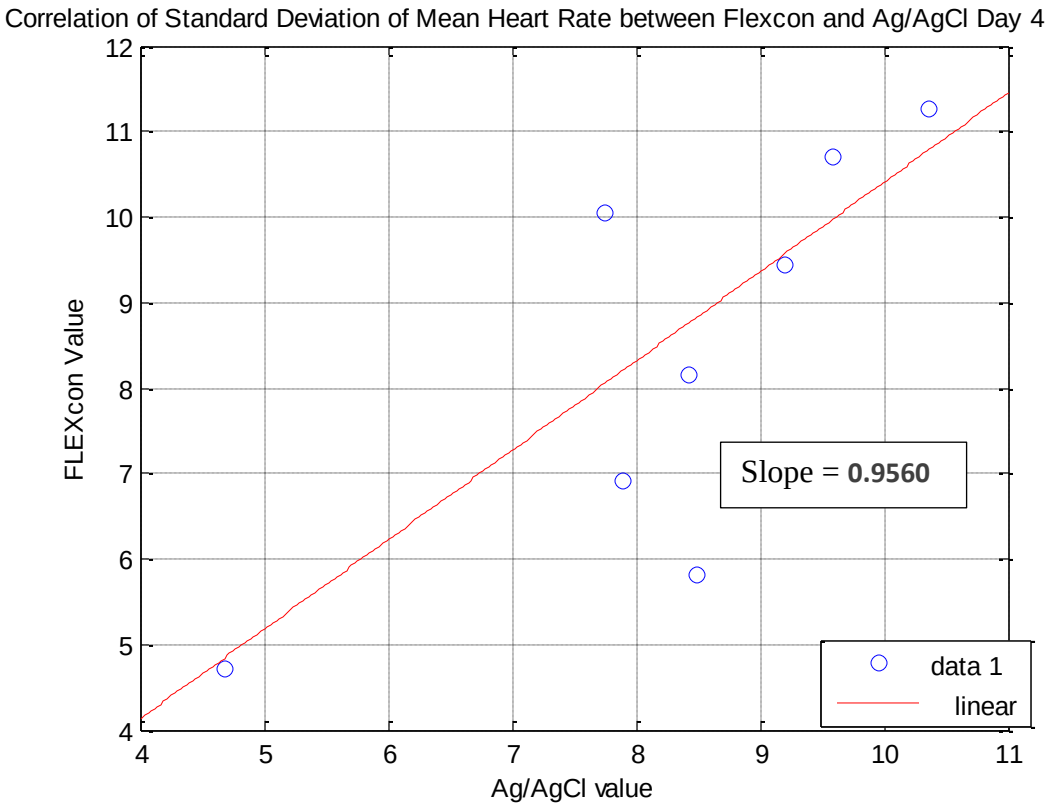


Figure 52: Correlation of STD of Mean Heart Rate for FLEXcon and Ag/AgCl, Day 4.

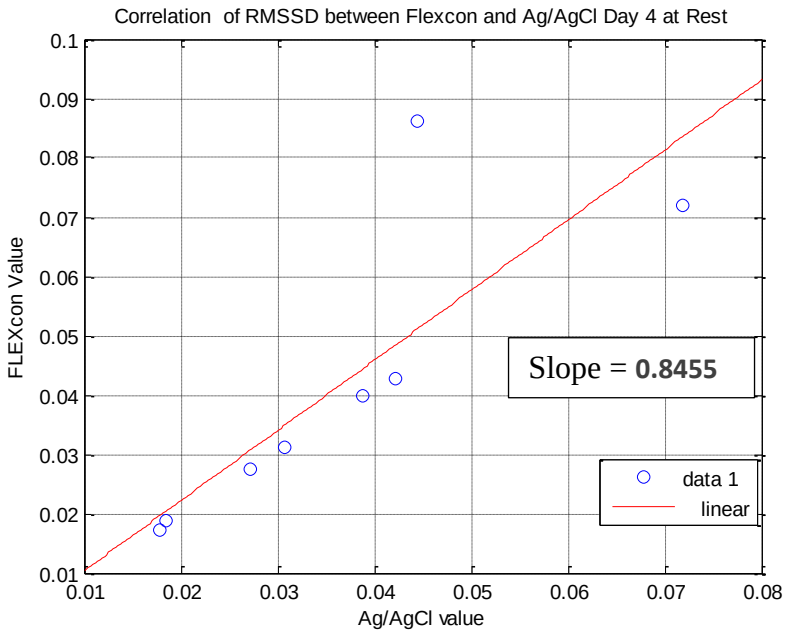


Figure 53: Correlation of RMSSD for FLEXcon and Ag/AgCl Day 4.

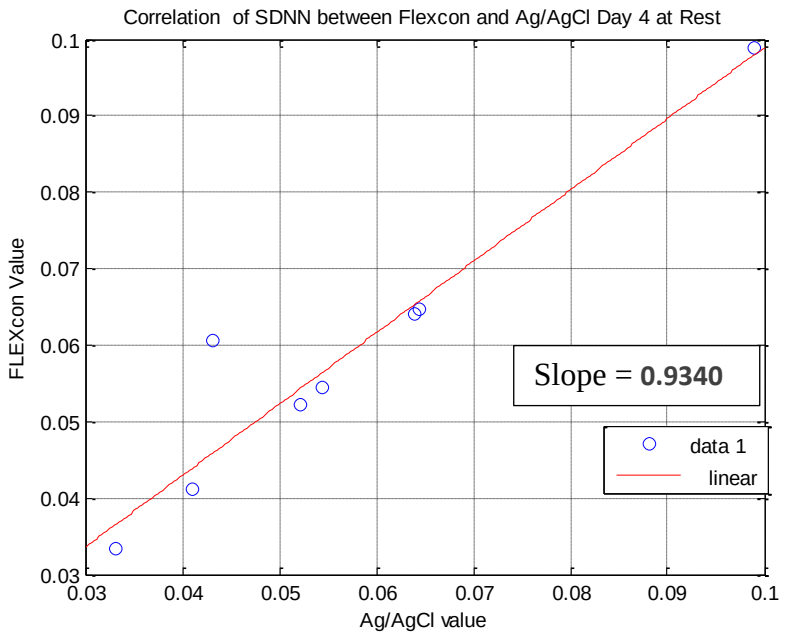


Figure 54: Correlation of SDNN for FLEXcon and Ag/AgCl Day 4.

The end of long term experiment is day 5 or after 96 hours. All electrodes were taped for all 10 subjects because the adhesion was not strong any more. After making sure that all electrodes had good conduction with skin data recording started for the last 15 minutes. At the end all electrodes were removed from 10 subjects and observed the skin. Pictures were taken after electrode removal. The pictures below shows the skin iteration and redness after 5 days of 96 hours. The subject below have the most skin iteration than other subjects. The adhesion of electrodes stuck on skin was removed with adhesive removal and clean the skin with alcohol pads. All the subjects were thanked for their participation on all experiments the MQP team designed.

Table 16: HRV Analysis for Day 5.

Subject #	fc_Found	fc_fixed	ag_found	ag_Fixed	LF_fc	LF_ag	HF_fc	HF_ag
1	193	0	193	0	1.09E+06	1.09E+06	2.54E+04	2.49E+04
2	162	0	162	0	8.23E+04	8.15E+04	4.37E+03	4.33E+03
3	136	0	136	0	6.85E+03	7.21E+03	1.74E+04	2.02E+04
4	166	0	166	5	2.46E+04	2.48E+04	3.05E+04	2.93E+04
5	175	0	175	8	2.44E+05	2.44E+05	5.13E+03	5.31E+03
6	172	6	172	2	2.76E+05	2.65E+05	3.81E+04	3.34E+04
7	156	0	156	0	3.30E+05	3.32E+05	9.59E+03	9.43E+03
8	166	0	166	0	2.32E+06	2.38E+06	2.02E+05	2.13E+05
9	169	0	169	1	2.00E+05	2.02E+05	500.9089	527.6969
10	193	0	193	0	8.86E+05	8.77E+05	1.27E+03	1.23E+03
				Average	5.45E+05	5.50E+05	3.34E+04	3.42E+04

Subject #	mean_bpm_f	mean_bpm_a	std_bpm_fc	std_bpm_ag	RMSSD_fc	RMSSD_ag	SDNN_fc	SDNN_ag
1	97.7743	97.7156	10.319	9.7049	0.0211	0.0213	0.0426	0.0426
2	81.8904	81.8599	7.7189	7.4813	0.0247	0.0243	0.0464	0.0464
3	70.1592	70.3568	21.685	22.7569	0.0382	0.0663	0.0469	0.0566
4	83.6781	83.6628	4.3046	4.3081	0.0353	0.0347	0.0396	0.0394
5	88.4267	88.4206	7.6698	7.6804	0.0206	0.0211	0.048	0.0481
6	86.8257	86.8165	5.2697	5.1134	0.0225	0.0224	0.0354	0.0352
7	78.9696	79.0672	9.6918	10.6845	0.0393	0.039	0.0596	0.0596
8	85.7377	86.1563	25.7153	30.9093	0.0375	0.0374	0.0691	0.069
9	84.8649	84.8637	4.1552	4.143	0.0163	0.0158	0.0325	0.0324
10	97.0086	96.9953	5.3153	5.2431	0.0106	0.011	0.0273	0.0273
Average	85.53352	85.59147	10.18446	10.80249	0.02661	0.02933	0.04474	0.04566

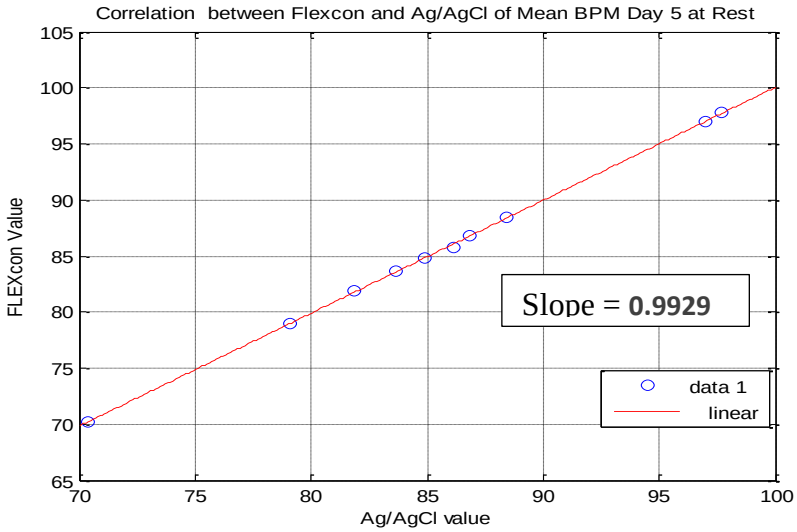


Figure 55: Correlation of Mean Heart Rate for FLEXcon and Ag/AgCl Day 5.

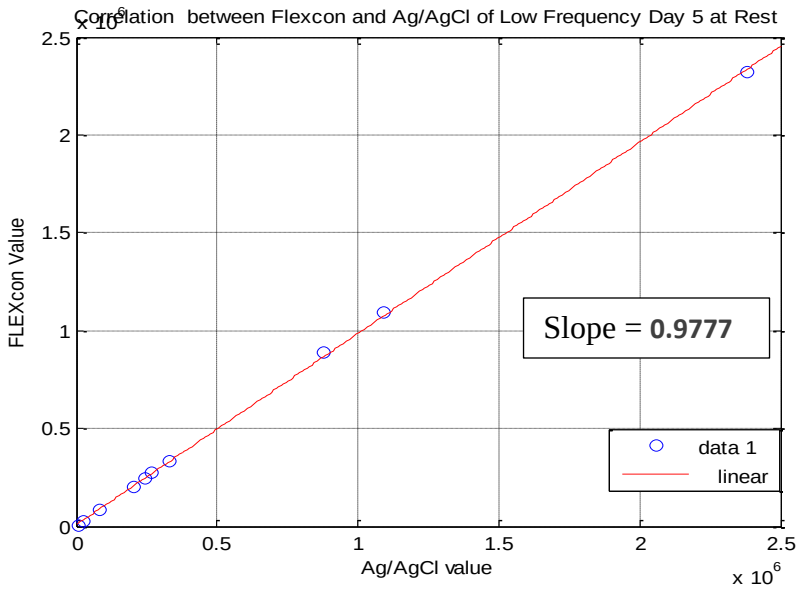


Figure 56: Correlation of Low Frequency for FLEXcon and Ag/AgCl, Day 5.

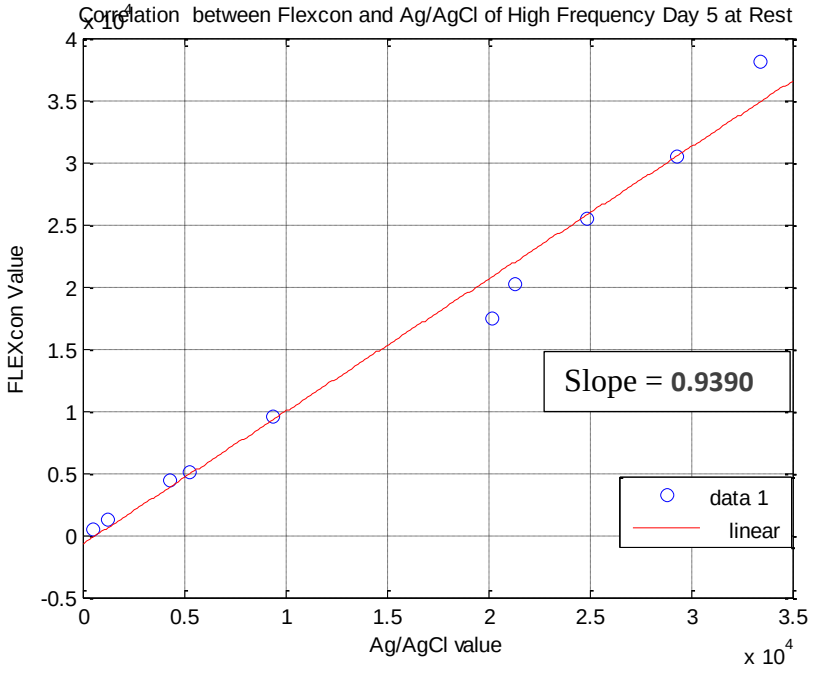


Figure 57: Correlation of High Frequency for FLEXcon and Ag/AgCl Day 5.

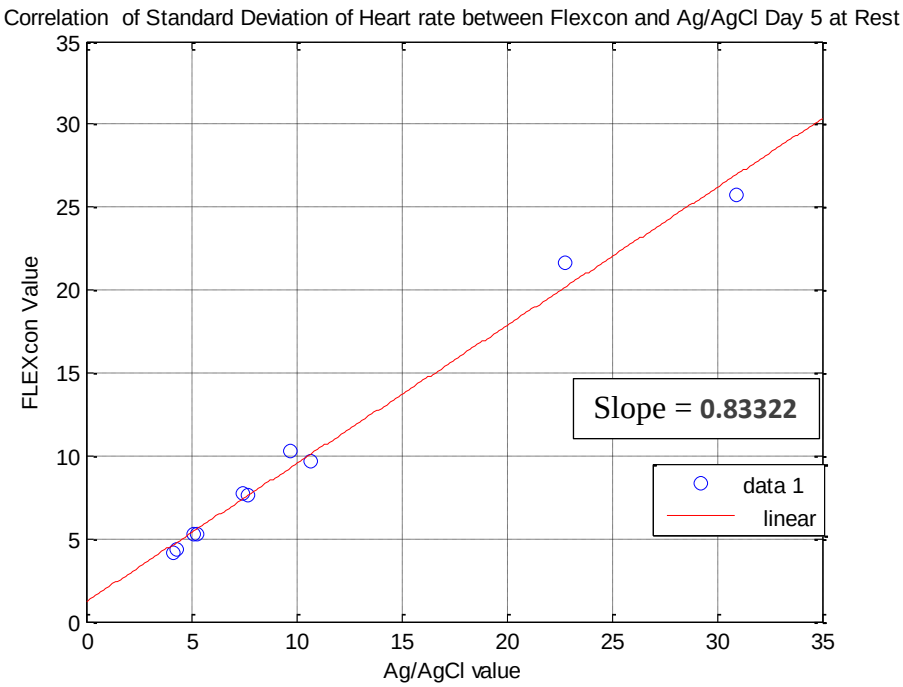


Figure 58: Correlation of STD of Mean Heart Rate for FLEXcon and Ag/AgCl Day 5.

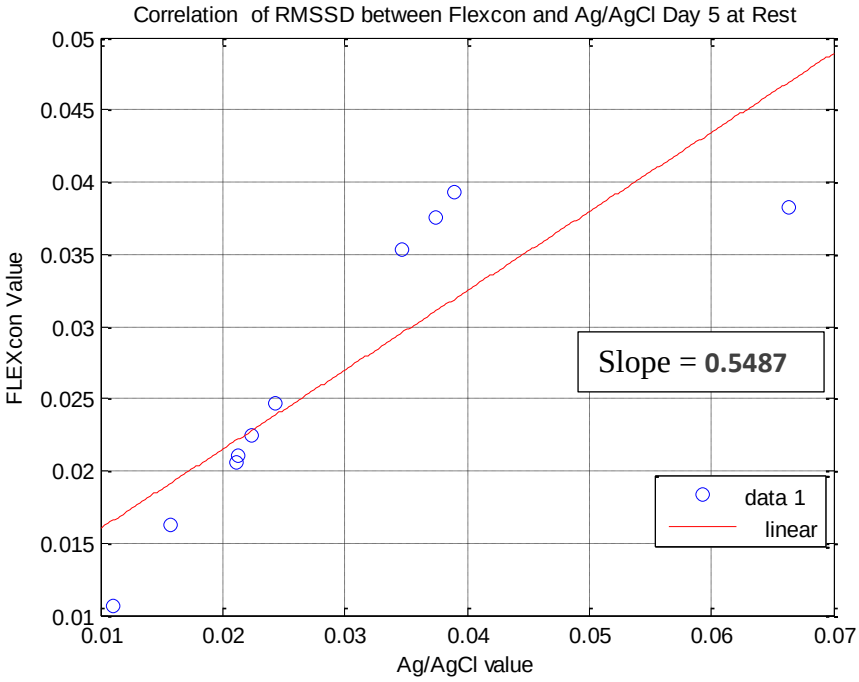


Figure 59: Correlation of RMSSD for FLEXcon and Ag/AgCl Day 5.

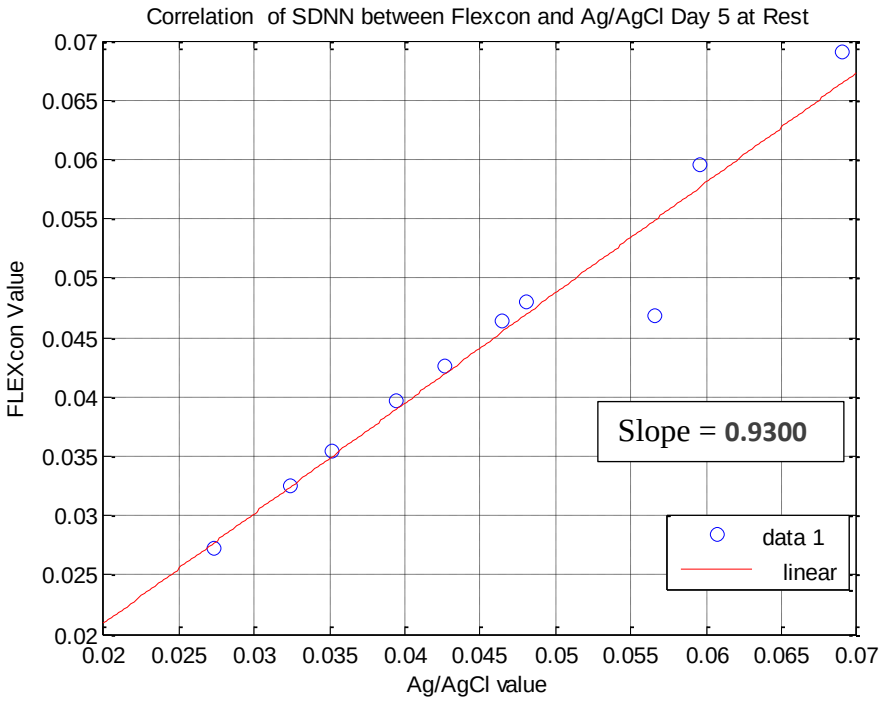


Figure 60: Correlation of SDNN for FLEXcon and Ag/AgCl Day 5.

Heart rate variability was analyze for each day for all 5 days. Also, at the end of day 5 of data analysis, it was done the HRV for all 5 days together. The correlation coefficient for entire data analysis are on last row of table below. Graphs for each variable were plotted, where FLEXcon values are on vertical axes and Ag/AgCl are on horizontal axes.

Table 17: Correlation Coefficient of HRV Analysis over period of 5 days.

	Correlation Coefficients for HRV					
	Mean_BPM	LF	HF	std_PBM	RMSSD	SDNN
Day1 Rest	**0.98978**	**0.99726**	**0.9467**	**0.9557**	**0.973**	**0.735**
Day2 Rest	**0.9894**	**0.9826**	**0.8919**	**0.9832**	**1**	**0.9867**
Day3 Rest	**0.97621**	**0.9635**	**0.95379**	**0.31166**	**0.9782**	**1**
Day4 Rest	**0.99569**	**0.9684**	**0.93799**	**0.29413**	**0.8455**	**0.934**
Day5 Rest	**0.99285**	**0.97768**	**0.939**	**0.83322**	**0.5487**	**0.93**
5 Days at Rest	**0.99651**	**1**	**0.933**	**0.76087**	**0.97716**	**0.9**

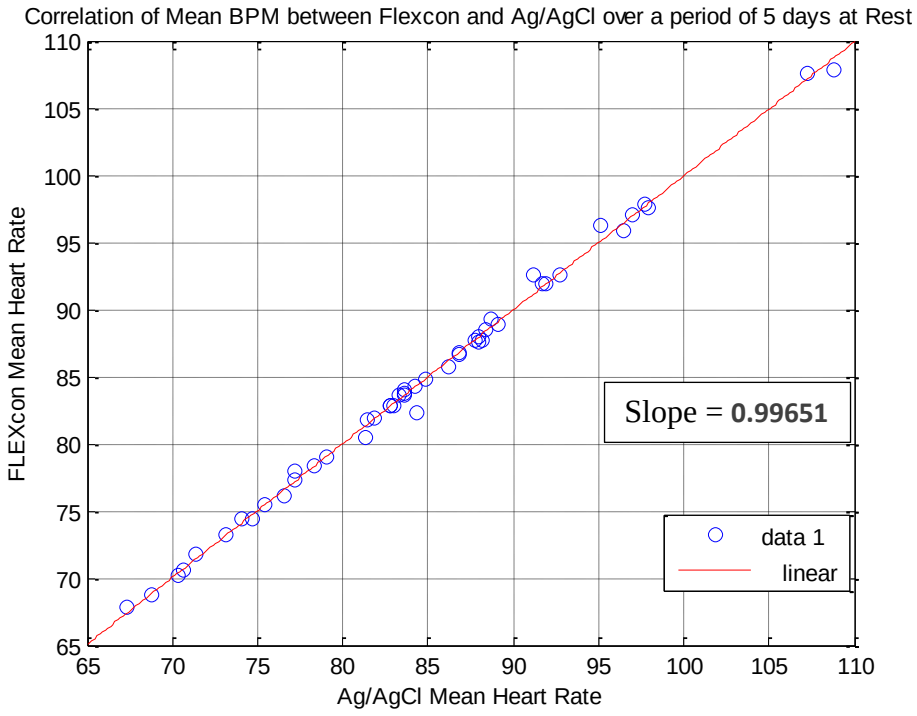


Figure 61: Correlation of Mean Heart Rate for FLEXcon and Ag/AgCl for 5 days.

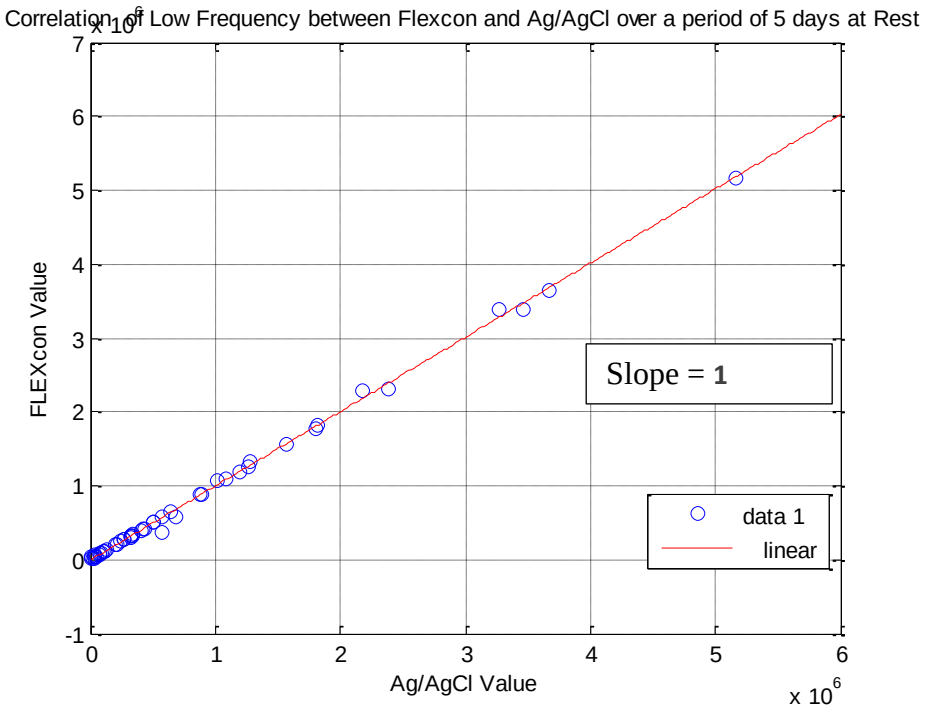


Figure 62: Correlation of Low Frequency for FLEXcon and Ag/AgCl, for 5 days.

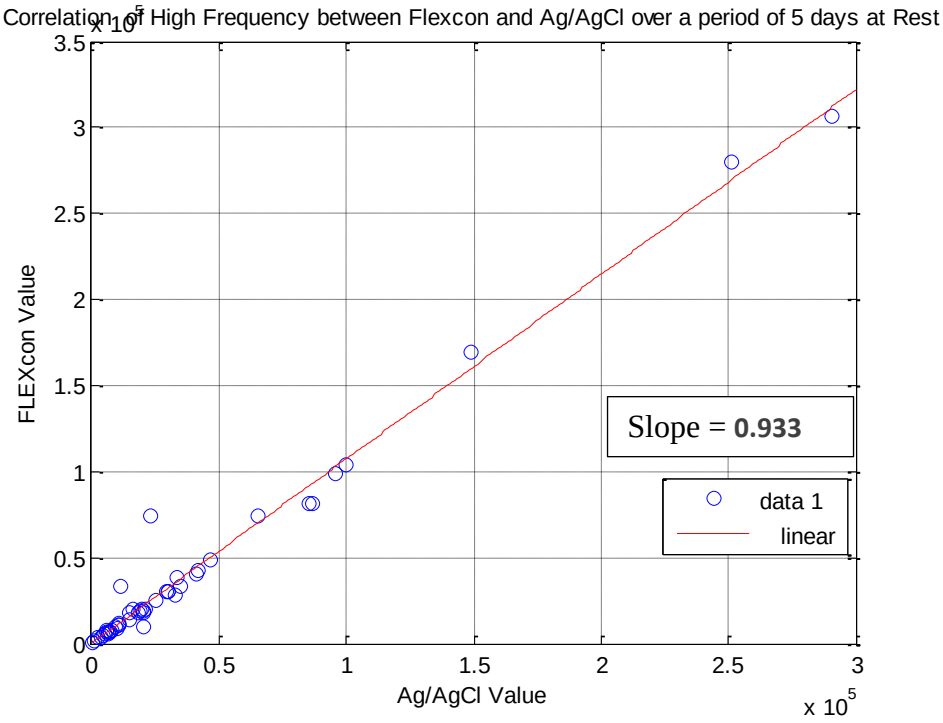


Figure 63: Correlation of High Frequency for FLEXcon and Ag/AgCl for 5 days.

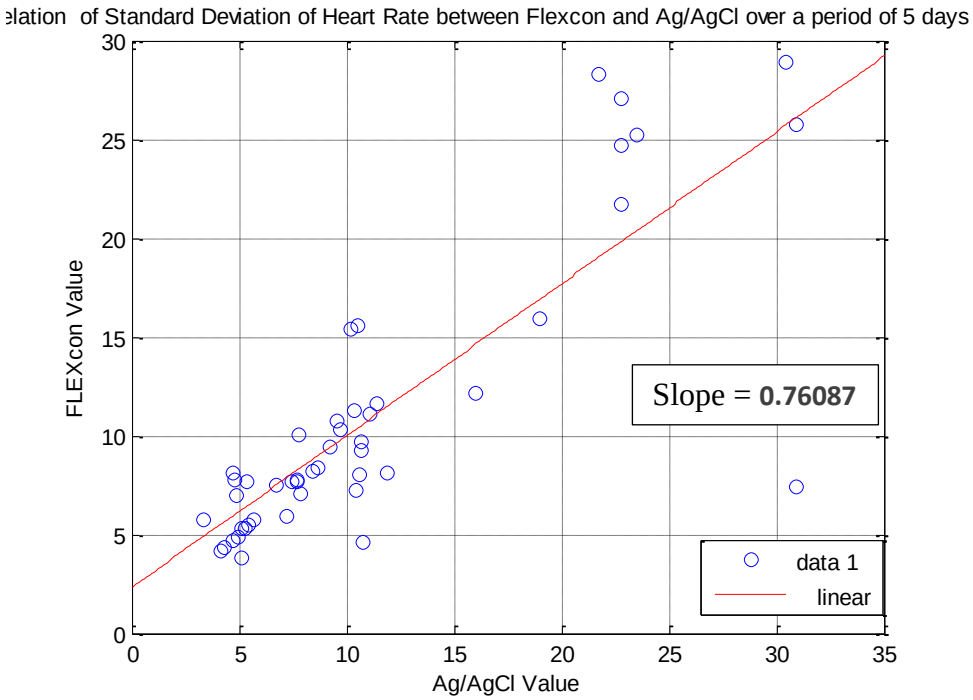


Figure 64: Correlation of STD of Mean Heart Rate for FLEXcon and Ag/AgCl for 5 days.

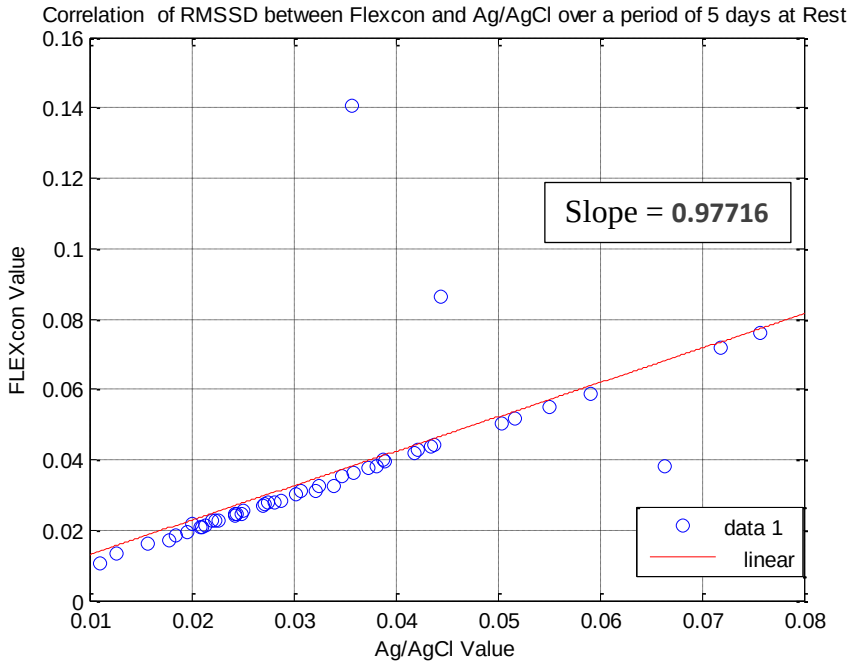


Figure 65: Correlation of RMSSD for FLEXcon and Ag/AgCl for 5 days.

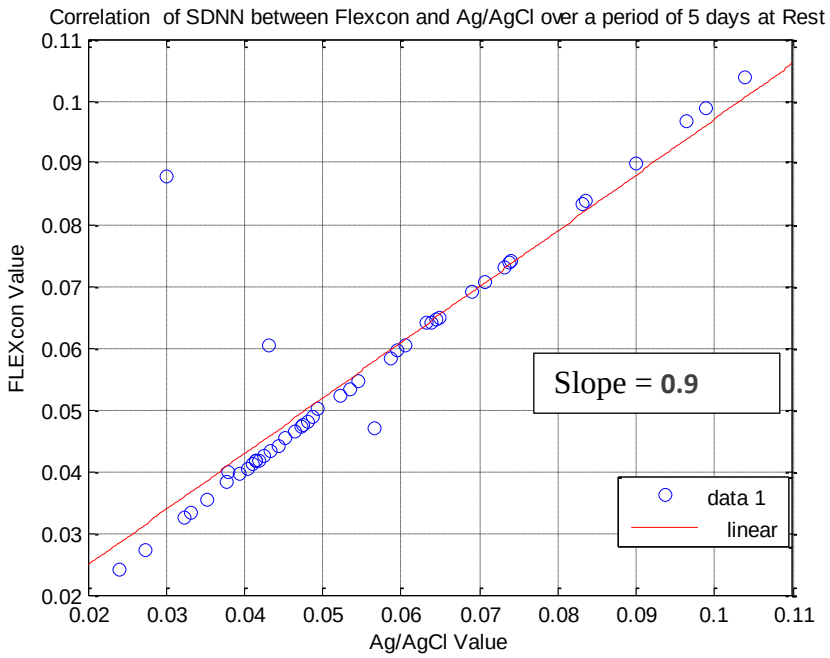


Figure 66: Correlation of SDNN for FLEXcon and Ag/AgCl for 5 days.

5.6 Phase II: Motion Artifact

During the long-term measurement of the subjects' ECGs, the subjects were required to remain seated, in a resting position, for five minutes. Then, the subjects were asked to walk around the facility for five minutes. Changes in ECG signal quality were measured via two methods: peak detection and Discrete Fourier Transform (DFT) analyses. Arbitrary 2-minute segments of the ECG during motion were analyzed.

The designed peak detection algorithm was utilized to count the number of QRS complexes; however, motion artifacts affected the quality of the ECG traces, causing misdetections.

Although the peak detection algorithm provided a concrete metric of electrode performance during resting, neither peak detection nor visual inspection could effectively facilitate the distinguishing of QRS complexes in traces that were affected by large-amplitude noise.

Therefore, the DFT was utilized as a secondary measure to analyze changes in signal quality. Because the Holter monitors sampled the human ECGs at 180 samples per second, the DFT was mapped to frequencies between 0 and 90 Hz.

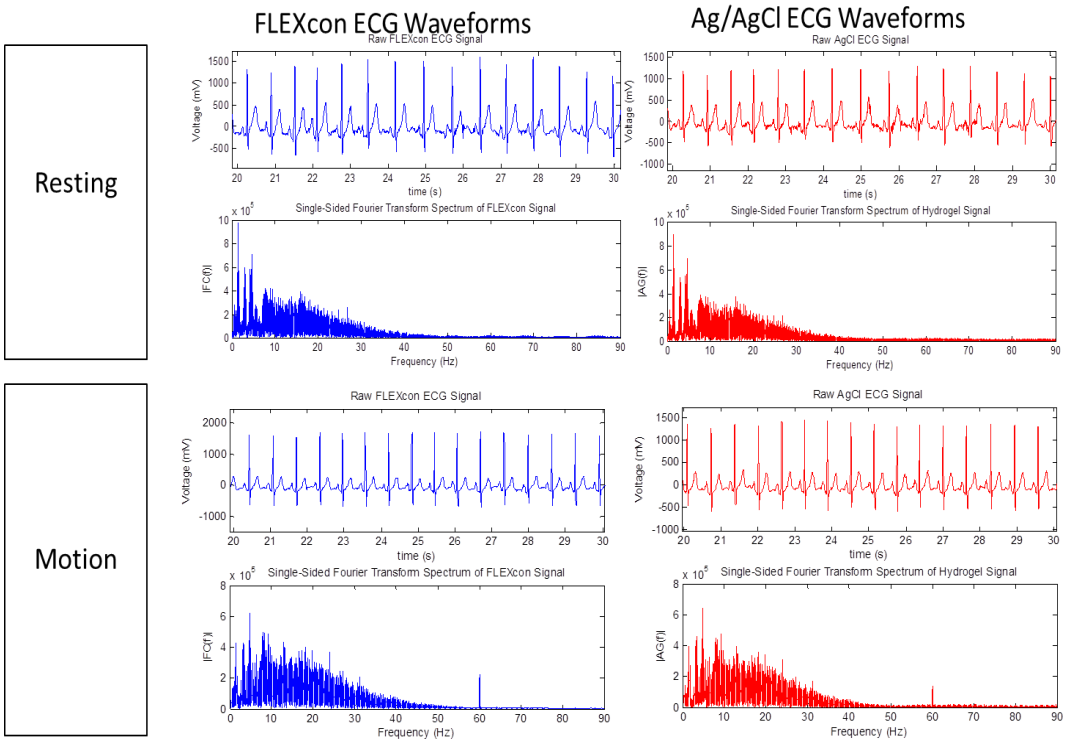


Figure 67: Time-domain and DFT analysis of a randomly selected human subject's ECG within 12 hours after initial electrode application.

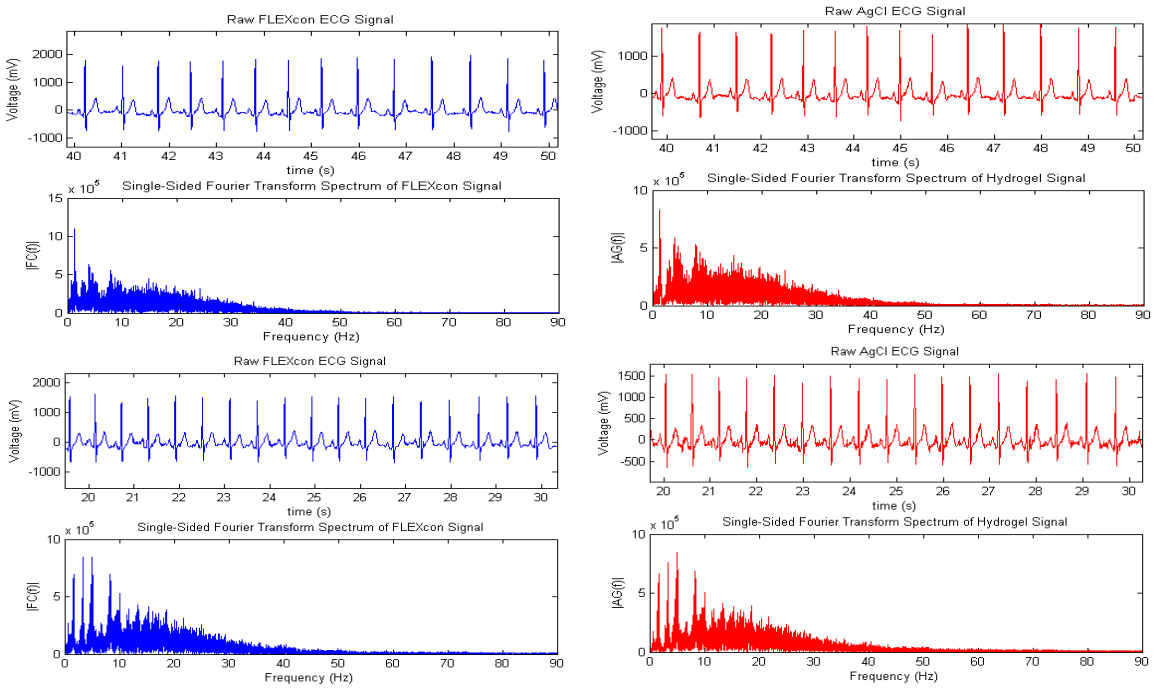


Figure 68: Time-domain and DFT analysis of a randomly selected human subject's ECG when stationary (top) and in motion (bottom), between 24 and 36 hours after initial electrode application.

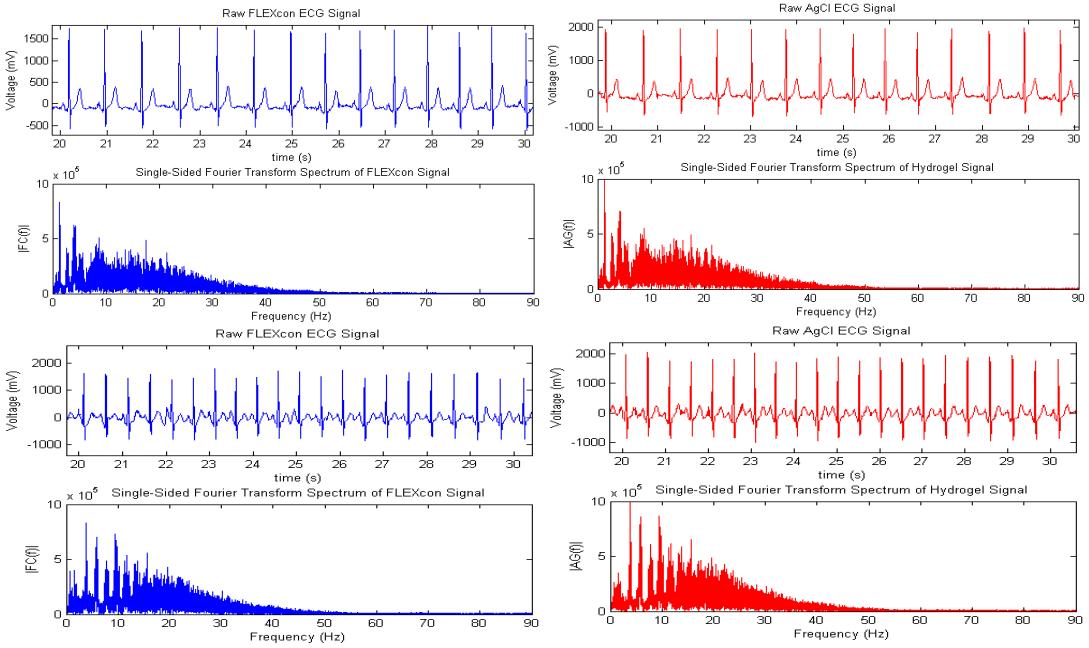


Figure 69: Time-domain and DFT analysis of a randomly selected human subject's ECG when stationary (top) and in motion (bottom), between 48 and 60 hours after initial electrode application.

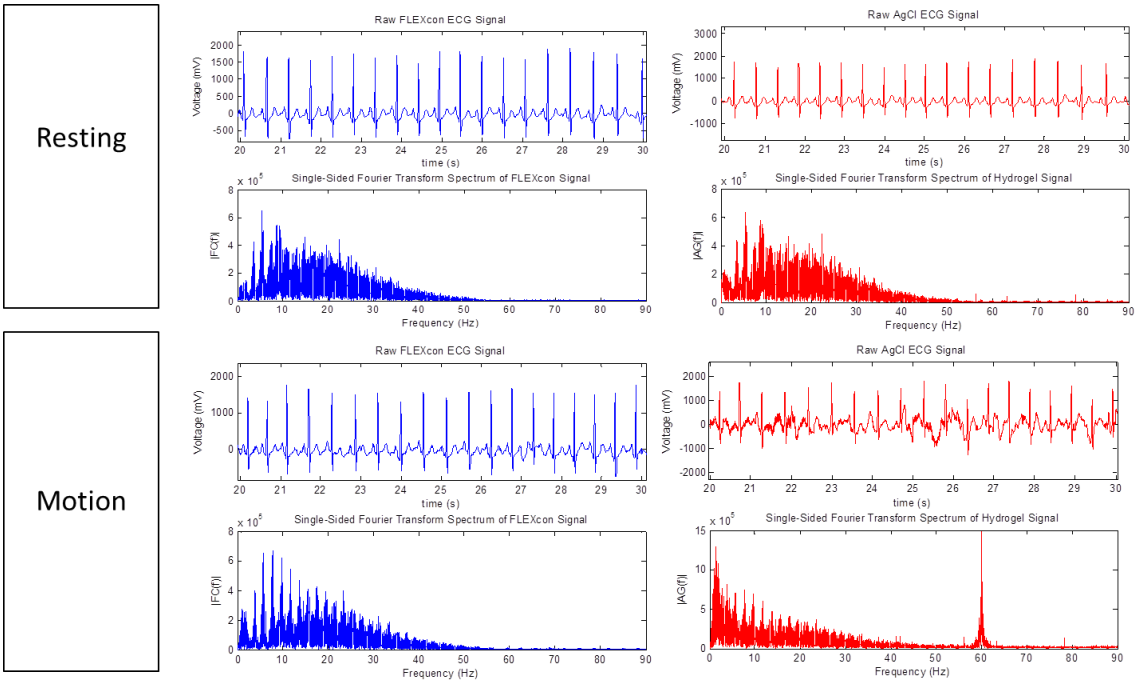


Figure 70: Time-domain and DFT analysis of a randomly selected human subject's ECG when stationary (top) and in motion (bottom), between 72 and 90 hours after initial electrode application.

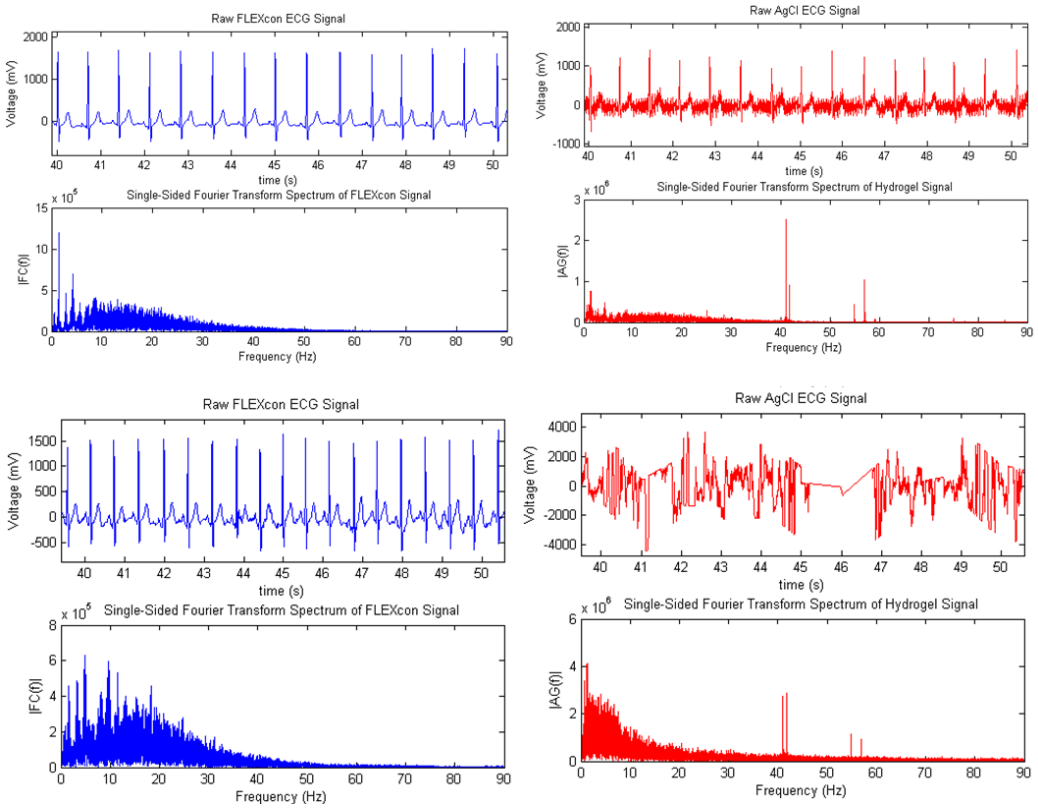


Figure 71: Time-domain and DFT analysis of a randomly selected human subject's ECG when stationary (top) and in motion (bottom), 96 hours after initial electrode application.

Chapter 6: Discussion

6.1 Introduction

Following experimentation, the first clinical study produced a variety of statistical, mechanical, and biomaterial results to characterize the strength and biocompatibility of FLEXCon's experimental adhesives. These experiments were designed to simultaneously characterize these measures generated by commercially available hydrogel electrodes, to provide a baseline performance benchmark.

6.2 Electrode Biocompatibility Analysis

The electrodes that had fallen off varied from subject to subject due to the adhesion between the skin tissue and the electrode. The Gen. 2-A electrode exhibited the strongest skin-to electrode adhesion. This electrode outperformed all the other types because only 2.5% had fallen off in the first four days, and only 7.14% had fallen off throughout the entire experiment, as shown in Figure 11. The Gen. 1 and Gen. 2 types showed stronger adhesion than that of the Ag/AgCl; however, Gen. 1 and Gen.2 caused severe skin irritation. Although Gen. 3 caused little to know skin irritation, it had the weakest adhesion to the skin.

The results of the long-term biocompatibility experiment (as shown in Figure 11) demonstrate that the G2-A adhesive was a superior option for further testing in Phase II. G2-A's skin adhesion data shows that it outperforms all types and the currently available on the market Silver/Silver Chloride (Ag/AgCl) by 43%.

6.3 Removal Force Analysis

During the force test, one FLEXcon was adhesive was compared to the AgCl hydrogel. These adhesive mediums were attached to two types of electrode body materials, cloth and polypropylene foam, to characterize the relationship between adhesion strength and electrode

body material type as well as compare the retention of adhesive strengths of FLEXcon's SRM and a standard adhesive after repositioning. These two primary metrics were measured for both pulling and peeling forces.

The pulling force experiment was designed to replicate ECG lead tugging forces that are caused by patient or equipment movement and compare the Ag/AgCl and FLEXcon adhesives' resistances to these forces. The mechanical force profile of these trials each showed the escalation to a single maximum force just before a rapid drop to zero, indicating the threshold force required to pull the electrode from the subject's skin. In the cases of both adhesive types, the rigidity and thickness of the adhesive affected overall resistance to tensile forces, as shown in Figure 12. The foam provided more mechanical stability for the adhesive, increasing the threshold removal force. As demonstrated in Figure 13, attached to the rigid foam body, the FLEXcon Adhesive required a larger removal force than that of the control adhesive; however, after repositioning, the FLEXcon adhesive was removed more easily. Attached to the soft fabric material, both the FLEXcon and control adhesives experienced equivalent losses in adhesive resistance.

Next, the force required to peel the electrode from the skin was measured. Unlike the pulling force profile, the peeling force measurement showed two maxima separated by a local minimum. The second maxima was immediately followed by a quick decrease to zero, indicated complete removal of the electrode from the skin. The first maximum was the force measurement of interest because it indicated the force necessary to overcome the adhesive bond between the entire electrode surface and the skin. Figure 14 shows that the forces required to peel the electrode is much smaller than that required to pull the electrode. The use of the fabric and foam bodies with the FLEXcon electrode further illustrated how more rigid materials provide more

support to a given adhesive. The Ag/AgCl electrode samples (attached to the foam material) provided an adhesion performance benchmark for comparison between experimental and commercially available adhesives. Although the performance index (control: experimental) was approximately one during the first removal, this ratio doubled after the second peel, indicating a decrease in the FLEXcon adhesive's strength, relative to that of the commercial adhesive (Figure 15). Therefore, the control adhesive maintains more of its adhesive integrity after repositioning.

This force study addressed factors that could cause complications during clinical implementation of the FLEXcon electrodes. Environmental factors and human error cause the removal or repositioning of the electrode. The pulling force experiment allowed the group to determine that the experimental adhesive is highly resistive to tensile forces that are present in dynamic environments. However, the adhesive loses approximately 80.5% of its mechanical strength after the first removal.

6.4 Storage Temperature and Electrode Performance

A three minute ECG signal was recorded for each subject. Figure 67 displays the average heart rate for all ten subjects. At 160 Fahrenheit the integrity of the signal for FLEXcon's electrode showed the same heart rate detection as the hydrogel with an average of 80.3 beats per minute (bpm). As well as the -80 Fahrenheit at 79.8 bpm. The results of the collected data before and after repositioning highlighted that the FLEXcon electrode had the same measured heart rate as the hydrogel and the rectitude of the signal was not compromised.

Further statistical variables and analyses for the collected data were performed by calculating the power spectral density (PSD) of both signals. From these PSD plots, the low-frequency signal powers (LF), high-frequency signal powers (HF) were calculated. In the time

domain, the root mean squared of standard deviation (RMSSD) and the standard deviation of R-R interval time length (SDNN) were used to determine the variance of heart rate.

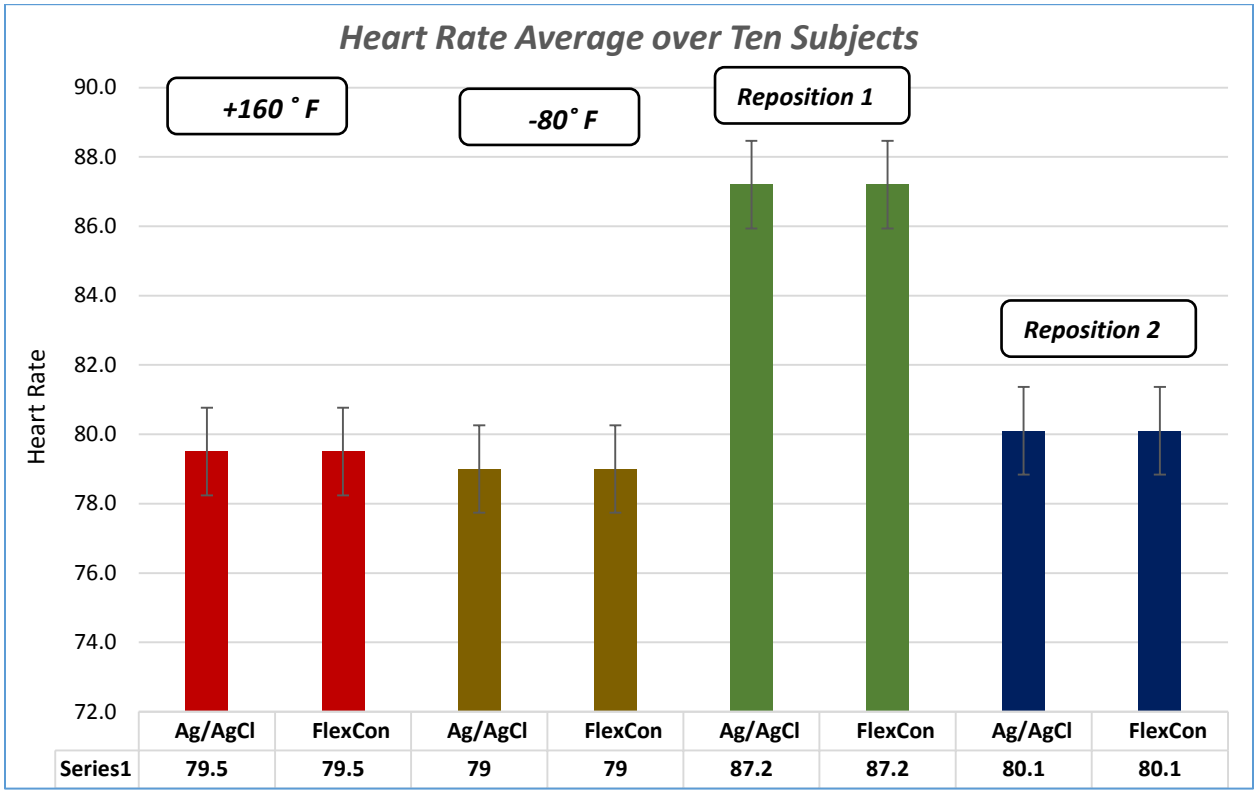


Figure 72: Average heart rate for ten subject.

The Root Mean Square of the Successive Differences it's an important tool in looking into the time domain in order distinguish the heart rate variability, and the RMSSD will allow us to look into the successive differences between the intervals of the two signals and compare them. Figure 68 shows the statistics of our data for RMSSD. Looking into 160^{o}F and -80^{o}F the calculated results manifest that the difference between the two signals is only 1%. This value is negligent since the detected heart rate would not have a significant difference in the measured heart rate. In Reposition 1 (R1) and Reposition 2 (R2) for the room-temperature electrodes the RMSSD statistical values highlights the equivalent values for hydrogel and FLEXcon.

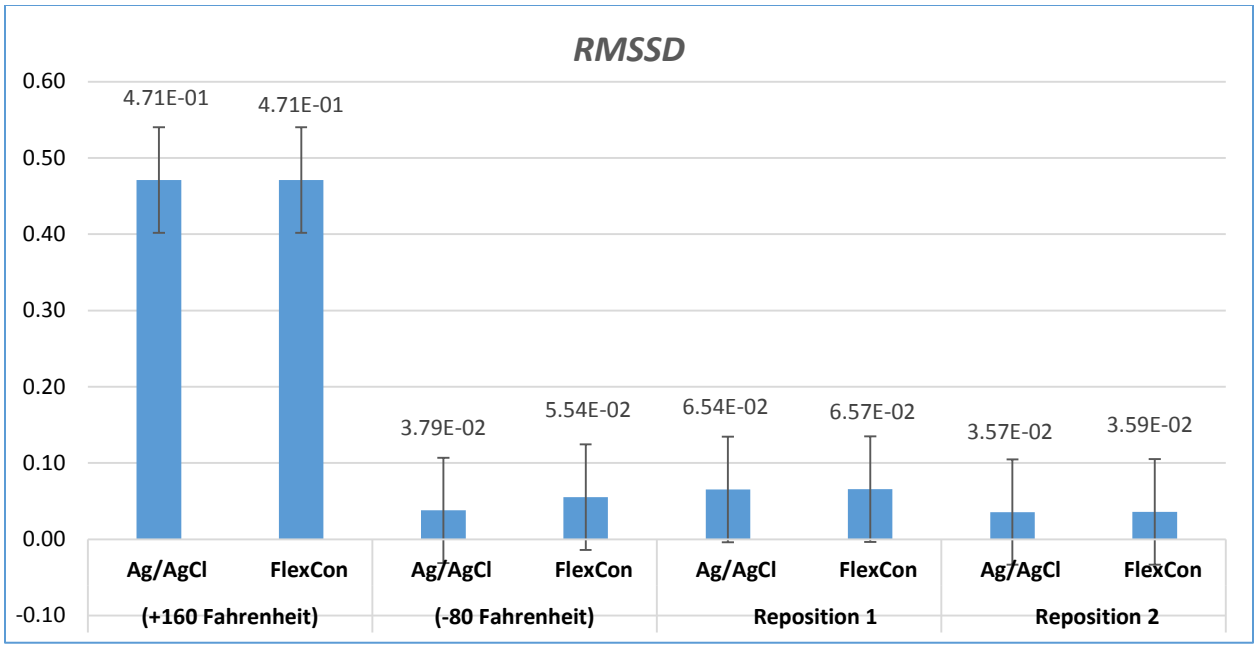


Figure 73: Statistical results for the root mean square for the successive differences.

Another important statistical comparison of the signal is the Low-Frequency and High-Frequency signal power. The heart rate variability (HRV) spectrum contains two major components, the high frequencies (0.14-0.40 Hz; P = 0.0002) and low frequencies (0.05-0.14 Hz; P = 0.0001) components. Using our designed algorithm we were able to filter the two signals and compare the FLEXcon LF and HF to those of the hydrogel. The statistical results show that both signals share the same results across all three short-term studies.

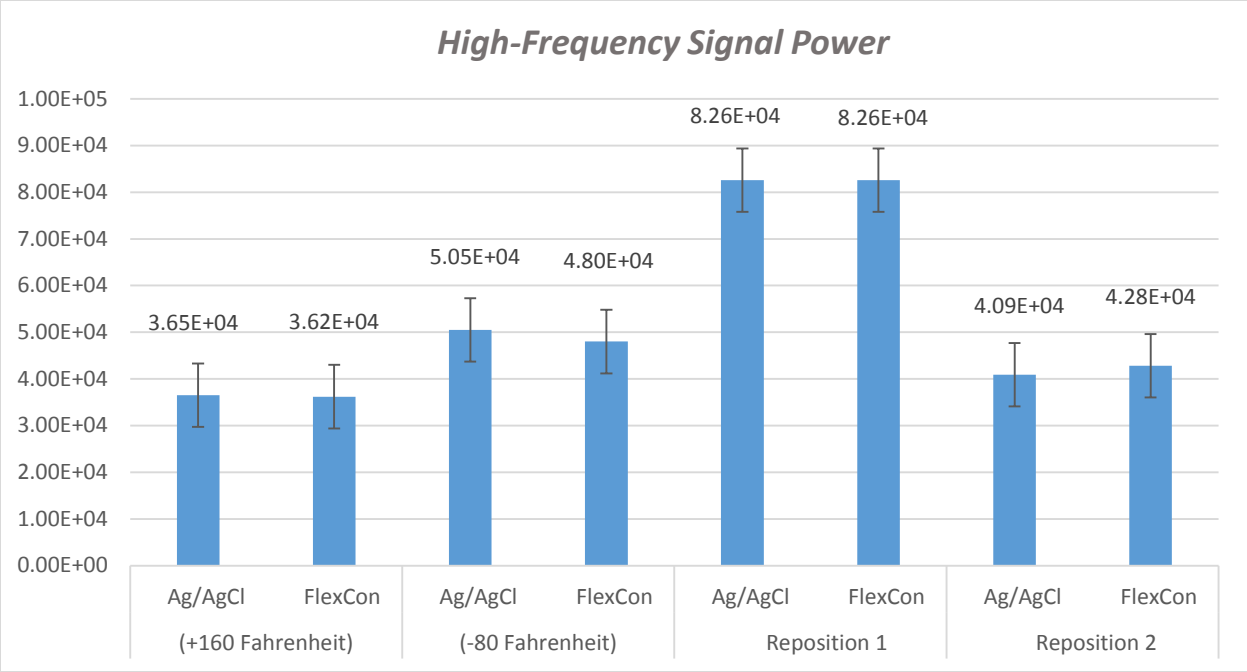


Figure 74: Statistical results for the High-Frequency signal power.

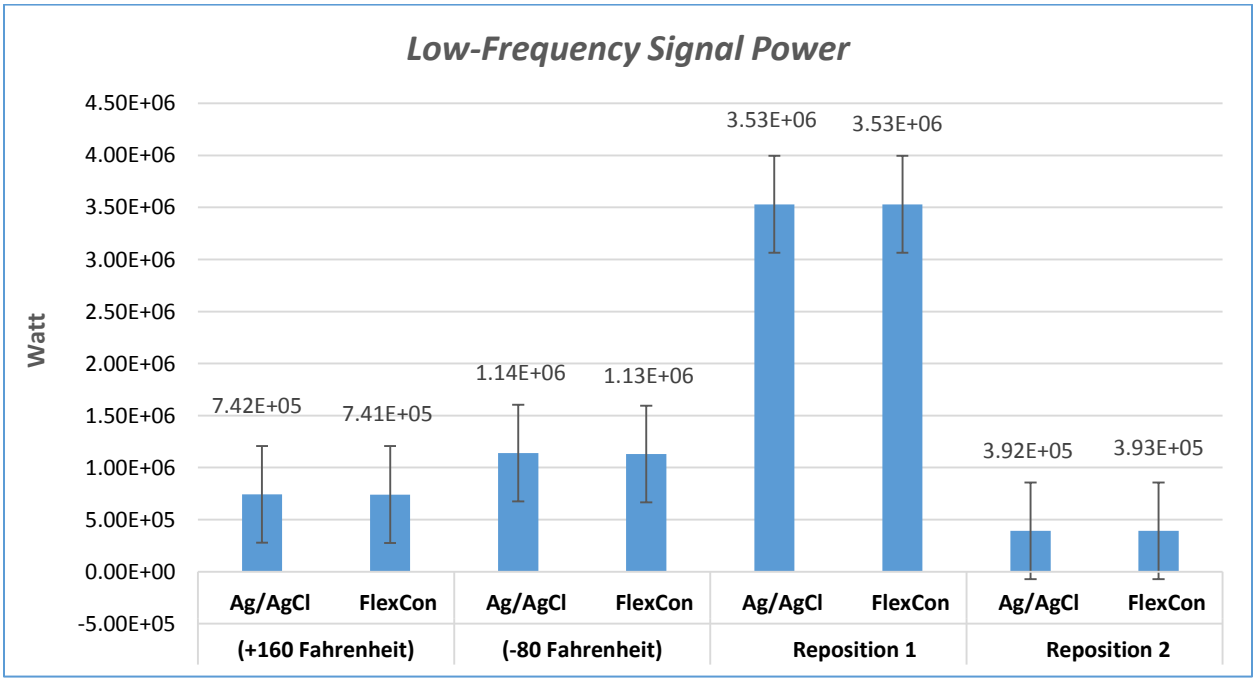


Figure 75: Statistical results for the Low-Frequency signal power.

Statistics for the standard deviation for the heart rate are shown below in Figure 71. In our analysis for the storage conditions and repositioning of the hydrogel and FLEXcon electrodes we can conclude that there is no statistical difference in the integrity of the signal. Both types of electrodes show no significant difference in the signal performance and heart rate detection without the concession of its functionality of the ECG. Furthermore, both types of electrodes show convincing results based on the signal performance and their functionality. An ECG signal is shown in Figure 71 below. Looking into the QRS complex wave of the two signals it was determined that the FLEXcon electrode is comparable to the hydrogel not only by looking into heart rate but also analyzing the statistical results of our data.

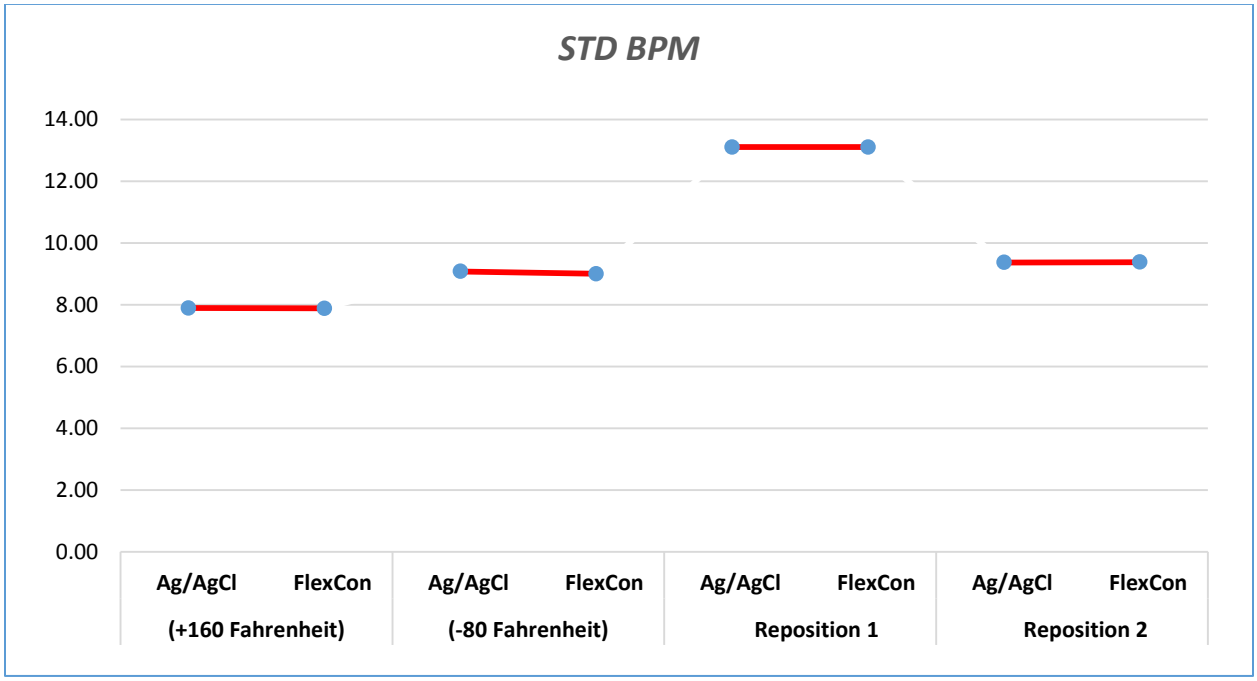


Figure 76: Statistical results for the Standard Deviation of heart rate.

6.5 Long-Term Resting ECG

Long term experiment was conducted over 5 days or 96 hours. This period of time was chosen from the results of Phase I. The correlation coefficient for all 5 days and for entire period of experiment are shown at table above. It is worth to mention the correlation coefficients for entire period. The mean heart rate is at 99.65 %. This result reflects a strong similarity between the FLEXcon and hydrogel signals. Low frequency LF of heart rate is at 100%, a perfect comparison. The correlation coefficients between the FLEXcon and hydrogel heart rate variance, high-frequency signal power, and SDNN were greater than 95%, demonstrating high correlation between the two electrodes.

6.6 Investigating Motion Artifact

The utilization of the DFT and peak detection algorithm showed changes in signal quality during long-term clinical ECG measurement. Throughout the progression of the clinical measurement, the ECGs measured by both FLEXcon and Ag/AgCl electrodes had defined QRS complexes. Figure 62 shows that shortly after electrode application, the signal quality in both the time and frequency domains are identical while the subject was at rest. The P, QRS, and T complexes are clearly defined in the time domain. In the frequency domain, both FLEXcon and hydrogel waveforms have three harmonic peaks in the 1-5 Hz band. The low-frequency content of the ECG signal is separated from the higher-frequency noise by a lower-amplitude valley within the 6-8 Hz band. During motion, both the FLEXcon and hydrogel signal DFTs reflect the removal of this valley, the increase in background noise bandwidth and amplitude, as well as the reduction of the signal-to-noise ratio between the three harmonic ECG peaks and the background noise. However, these artifacts are not large enough to cause significant distortion of any of the ECG waves in the time domain.

Twenty-four hours after initial electrode placement, stationary ECG measurement still exhibited clear waveform definition, as shown by three DFT peaks, between 1 and 5 Hz, with amplitudes significantly above noise level (in Figure 63). However, motion introduced significant 9-Hz and 10-Hz artifacts in both FLEXcon and hydrogel measurements. As a result, both ECGs exhibited low-amplitude and high-frequency fluctuations in the P and T waves and retained QRS complex definition.

Fourier analysis of ECG signals 48 hours after the start of the experiment showed further definition of motion artifact interference in both FLEXcon and hydrogel measurements. Figure 64 demonstrates the formation of 5 higher-frequency (8-15 Hz) noise maxima of magnitudes comparable to those of the signal peaks (1-5 Hz). This formation of larger-amplitude, higher-frequency motion artifacts resulted in the increase in P wave amplitude and the decrease in T wave amplitude.

Seventy-two hours after electrode application, the P and T waves were defined by distorted during the resting measurement. A single artifact at 10 Hz was evident above background noise level in both stationary measurements. However, during motion, low-frequency distortion in the FLEXcon signal caused further increase in P wave amplitude and the reduction of T wave amplitude. The ECG measured by the hydrogel electrodes exhibited significant low-frequency interference – in the time domain, there was little to no P and T wave definition. The hydrogel electrodes exhibited high sensitivity to 60-Hz power line interference, whereas the FLEXcon ECG did not (Figure 65).

Lastly, after 90 hours of use, the FLEXcon electrodes maintained QRS complex definition with some distortion of the P and T waves. In contrast, the hydrogel electrodes produced significant high-frequency noise artifacts during resting measurements. In the

stationary hydrogel ECG signal, the P and T waves were indistinguishable (Figure 66). During motion, sensitivity of the hydrogel to low-frequency baseline wander is evident in both the time and frequency domains; the motion of the subject caused power rail saturation, completely distorting the entire ECG waveform.

Chapter 7: Final Design and Validation

7.1 Introduction

Atrial fibrillation is a common form of cardiac arrhythmia that results in rapid, weak atrial quivering. The inability of the atria to deliver blood to the ventricles can result in the clotting of stagnant blood and subsequent onset of stroke. This cardiac abnormality is common in the United States and becomes more frequent with increasing age (Centers for Disease Control and Prevention, 2013). In 1998, an estimated 2.2 million Americans were diagnosed with intermittent atrial fibrillation; in conjunction with pre-existing health complications, such as high blood pressure, diabetes, and histories of smoking, atrial fibrillation can cause death or serious internal injury (Benjamin et al, 1998).

Because atrial fibrillation is an intermittent disease, long-term electrocardiogram (ECG) measurement is necessary to detect potentially life-threatening episodes. In recent years, innovations in electronics, adhesives, and algorithm designs have contributed to the improvement of long-term cardiac monitoring systems. Noninvasive ECG measurement eliminates the risk of infection or injury; however, the measurement of the ECG on the surface of the skin introduces sensor-to-skin motion artifacts and environmental interference. Devices use analog amplification and filtering techniques to eliminate these different types of artifacts and facilitate ambulatory ECG measurement (Goette et al, 2011). The limited precision of analog components can allow some signal interference to continue to corrupt the signal. The utilization of digital signal storage allows thorough post-processing to further enhance ECG signal quality (Pan and Tompkins, 1985). The improved signal quality allows metrics – such as heart rate – to be accurately measured.

Although electrical component design and algorithm implementation can improve signal quality and facilitate the analysis of physiological signals, the electrode sensor itself is an important component of the ECG measurement that significantly impacts signal quality when there is insufficient adhesion to the skin (Nemati et al, 2012). The Ag/AgCl electrode, the standard of noninvasive ECG measurement, utilizes a hydrogel medium to translate ionic charge movement through tissue into electrical current. However, these electrodes are used for no longer than 48 hours at a time during Holter monitoring due to the causation of skin irritation and the reduction of signal quality due to the drying of the hydrogel.

To improve long-term sensor performance, FLEXcon USA © has produced an electrode that does not require quickly-drying gels to measure the ECG from the skin surface. This electrode design uses a patented Pressure Sensitive Adhesive (PSA) to promote high surface area skin-to-electrode adhesion. These electrodes require electrophoretic activation prior to clinical use, due to biocompatibility regulations established by the Association for the Advancement of Medical Instrumentation (AAMI), to limit sensor impedance. Last year's Major Qualifying Project (MQP) designed a method by which to evaluate the compliance of the FLEXcon electrode with AAMI standards and the electrical short-term performance versus that of the standard Ag/AgCl electrode.

This year, the current MQP group designed and conducted a method of clinically comparing long-term FLEXcon and Ag/AgCl electrode performances. This procedure addressed the numerous obstacles of physical and electrical interactions between the electrode and the skin, such as skin-to-electrode adhesion, repositionability, skin irritation, and ECG signal quality. The collaboration with FLEXcon to develop a biocompatible, strongly adhesive, and signal receptive

ECG electrode design will provide a means of ensuring high-quality, long-term, and in-home vital sign monitoring of arrhythmia-susceptible patients.

7.2 Project Organization and Design

A series of clinical studies – encompassing an array of implemented measurement systems – was designed to provide a comprehensive functional analysis of FLEXcon adhesive performance in clinical settings versus that of the standard Ag/AgCl hydrogel. This overall objective was divided into a series of three stages or phases, as shown in the project design Gantt chart (Figure 7) and work breakdown structure (Figure 8). After discussing the needs of the client (FLEXcon), the group refined its project design to compare the physical limitations of the client's four adhesive samples and determine which sample can exhibit a biocompatibility comparable to that of the Ag/AgCl electrode. After selecting a biocompatible electrode design, the MQP group developed a protocol to simulate long-term clinical vital sign monitoring. Then, a peak detection algorithm was designed to quantify ECG trace quality and compare the long-term signal acquisition capabilities of the FLEXcon and hydrogel electrodes.

7.3 Methods: Phase I

First, the client needed a means by which to determine the biocompatibility and physical limitations of four novel adhesive types. This clinical study was designed to recruit an ethnically diverse population of 10 human subjects, to reflect the diversity of the human population. Then, an experiment was conducted to correlate adhesion strength loss during repositioning to adhesive and body material type. CES EduPack, a material properties database, was utilized to select a list of materials that could be feasibly attached to a FLEXcon adhesive or hydrogel. Two of these materials – a rigid polypropylene foam and a flexible fabric material – were selected as substrates to be attached to a hydrogel and a FLEXcon adhesive. After sanitizing each subject's

skin, an each preliminary electrode design was applied to each subject's forearm. A manual tensile force transducer (National Instruments) was utilized to apply peeling and pulling forces via a metal wire connection and measure the maximum force required to remove each electrode from each subject's forearm before and after electrode repositioning.

Next, a second experiment was designed to quantify the irritation induced by wearing the standard and FLEXcon adhesives. In this procedure, 4 FLEXcon adhesives and one hydrogel adhesive were attached to rigid foam bodies. Then, 7 of each electrode design were applied to each of the 10 subjects' forearms after sanitizing the skin with ethyl alcohol prep pads. These subjects were instructed to not exercise during this 7-day clinical study. Then, every 24 hours, the subjects returned to the laboratory and completed a questionnaire to describe any experienced itchiness. The number electrodes that had fallen off of the subject in the past 24 hours was noted at the beginning of every session. Next, an electrode of each adhesive type was removed from each subject's forearm, and any changes in coloration were noted. If either the itchiness or skin coloration started to become abnormal, all of the electrodes containing the irritating adhesive were removed.

The results of this biophysical study showed that a combination of carbon nanotubes, small concentrations of ionic salt, and a thick adhesive caused little to no skin irritation during the 7-day experiment. This superior FLEXcon adhesive was subsequently tested for long-term signal quality.

7.4 Methods: Phase II

FLEXcon supplied electrodes consisting of either a novel adhesive or hydrogel signal receptive medium (SRM) attached to a polypropylene body material. Then, two experiments were conducted to create two correlations between adhesive type and ECG signal quality.

The first experiment utilized the short-term ECG to measure signal quality as a function of electrode storage temperature. Both the FLEXcon and hydrogel electrodes were stored at -80F, 160F, and room temperature for 72 hours (3 days) prior to use. Then, an ethnically diverse population of 10 subjects was recruited. Each subject was asked to sit in a seat and relax prior to the initiation of the study procedure. Then, each subject's lower left abdomen in upper chest were cleansed with ethyl alcohol to remove any dead skin. After allowing the ethanol to evaporate, a FLEXcon electrode and a hydrogel electrode that were stored at room temperature were placed on the upper left and upper right chest, as well as on the lower left abdomen. These sets of electrodes were connected to a BIOPAC system that was used to measure each subject's resting ECG for 3 minutes. Then, the electrodes were removed, the skin was cleansed, and the 3 lead ECG was measured again using the electrodes stored at 160F and -80F. All ECG data was stored in a computer post-processing.

After the conclusion of this experiment, the subjects participated in a second clinical long-term experiment. This procedure was designed to use FLEXcon and hydrogel electrodes to measure the 5-lead ECG simultaneously over the course of 5 days (96 hours) to simulate long-term vital sign monitoring.

First, each subject's skin was cleansed with ethyl alcohol prep pads. After waiting 60 seconds for the ethanol to evaporate, palpation was used to place a hydrogel and a FLEXcon electrode on each of 5 locations of the subject's thorax: the lower right and left abdomen, the upper left and right chest, and the manubrium sterni. Then, a Holter monitor was connected to each set of electrodes via shielded leads. Each subject was subsequently attached to relax and sit in a chair for 5 minutes. Then, the subject was allowed to walk around the facility for 5 minutes.

The Holter monitors were powered off after data collection, and the measured data was stored in a computer for post-processing.

Next, an algorithm was designed to detect QRS complexes and measure heart rate in each stored ECG trace (Pan and Tompkins, 1985). The program utilized a series of digital filters to locate the time indices of the ECG signal R waves. First, the ECG signal was processed with a band-pass filter that removed extraneous environmental noise. Then, a derivative filter was implemented to accentuate the sharp voltage transitions that take place in the QRS complex due to rapid ventricular polarization and depolarization. The output of this filter was subsequently squared to reduce the amplitude of residual high frequency and low-amplitude noise. Finally, a hamming window average filter was used to generate a signal with maxima at the R wave peaks.

Next, a threshold was applied to the output of the moving average filter to generate a square wave. The waveform has a value of 1 at time indices when the moving average waveform is above threshold and has a value of zero when the moving average output is below threshold. Then, a new waveform was generated to detect one-to-zero and zero-to-one transitions in the square wave. From this derivative waveform, the boundaries of peak-searching domains were established. A series of logical circuits were used to find the times (in seconds) at which the moving average waveform has maxima within the peak-searching bounds.

After the storage of these peak location times in a single array, the heart rate of the waveform was calculated. First, the derivative of this time index array was calculated, producing an array of R-R intervals (in seconds per beat). The instantaneous heart rate was calculated with the following relation.

Equation 8

$$:HR(i) = \frac{1}{R{-}R\ interval(i)} * 60 \frac{seconds}{minute} = beats\ per\ minute$$

Lastly, the average of these instantaneous heart rate measurements was calculated to determine the average heart rate.

This algorithm performed these operations on both the FLEXcon and hydrogel ECG waveforms. The heart rate metric was utilized to quantify the functional differences between the two electrode designs.

Chapter 8: Conclusions and Recommendations

8.1 Conclusions

The two designed clinical studies effectively characterized electrode performance and helped the client improve its adhesive design. The first study focused on the measurement of mechanical stability and adhesive-to-skin interaction during use in a long-term vital sign monitoring environment. After establishing physical limitations of the client's and industry standard adhesives, the second study was conducted to quantify ECG signal quality during both electrodes' effective periods.

The first clinical study established a preliminary biocompatibility benchmark that was utilized to select the least irritating and most mechanically stable adhesive of the client's four presented formulas. The results of this study demonstrated that the Generation 2-A adhesive caused little to no irritation (with minor itching) and experienced minimal electrode-to-skin adhesion loss during a 7-day period. A short-term tensile force measurement protocol showed that polypropylene foam sufficiently provided the rigidity necessary to maintain electrode form in response to lead force retention.

The second clinical study compared the ECG measurement capabilities of FLEXcon and hydrogel SRMs. An experiment was performed to determine the effect of temperature storage (72 hours) on ECG signal quality; reduction of P, Q, R, S, and T wave definition indicated loss of signal quality. The results demonstrated that temperatures between -80F and 160F did not cause significant differences in signal quality between the two tested adhesives. Then, a 4-day (96-hour) dynamic ECG measurement was conducted to observe changes in ECG signal definition in response to time and motion. The results of this experiment showed that while the subjects were at rest, both the FLEXcon and hydrogel electrodes maintained QRS complex

definition comparable to that of the standard hydrogel electrode throughout the 96-hour testing period. Utilization of the DFT to visualize motion artifacts during this 96-hour period showed that the FLEXcon electrode allowed frictional motion artifacts to reduce P and T wave definition. In comparison, the standard hydrogel dampened these motion artifacts more effectively during the first 48 hours; however, after 72 hours of use, the lack of moisture in the hydrogel sponge caused a more significant reduction of P and T wave definition and higher susceptibility to 60 Hz power line interference.

Although both electrode types showed R wave amplitudes significantly above noise level, occasional high-amplitude, high-frequency motion artifacts caused the utilized peak detection algorithm to incorrectly identify R waves and incorrectly measure instantaneous heart rate. The use of a regression line to correlate the heart rates measured by FLEXcon and hydrogel electrodes during both resting and ambulatory positions showed that the correlation coefficients were equivalent (0.997). Both correlation coefficients were greater than 0.95 ($p < 0.05$), demonstrating statistically similar performance results between the two electrode adhesive types.

8.2 Recommendations

The primary metrics of electrode performance during the second clinical study were average heart rate, heart rate variances, and rates of heart rate changes. All of these measurements were calculated based on the detection of R-R intervals via R wave detection, illustrating how well the tested electrodes facilitate basic clinical heart rate measurement. Thus, the prominence of the R-wave above noise determined whether the algorithm could measure the subject's heart rate. In future work, peak detection based on other waves in the ECG can show how well the FLEXcon and hydrogel electrodes exhibit waves and complexes other than those found in the QRS complex. The ability of FLEXcon electrodes to accurately and precisely

measure subtle cardiac anomalies that may not impact the R wave during long-term vital sign monitoring could provide important information to clinicians and ultimately save more lives.

At the conclusion of this long-term experiment, the electrodes were removed from the subjects' skin. Redness and accumulation of oils were observed on the entire areas of contact between the hydrogel electrodes and the skin; only redness was observed on areas of contact between the FLEXcon electrode's central signal-unifying bridge and the skin. This discoloration demonstrated that the bridge was inducing frictional shear on the skin and therefore introducing motion artifacts into the measured ECG. Thickening of the FLEXcon adhesive barrier would reduce friction (reducing the P and T wave distortions) as well as reduce sensations of skin discomfort and irritation.

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Appendix

```
%%Peak Detection Algorithm
clc; clear all; close all;
%% Read data
data = load ('S7_R1.txt'); % Load data collected with Biopac system
fc = data(:,2); %FLEXcon electrode data in second column, in Volts
ag = data(:,1); %Ag/AgCl electrode data in first column, in Volts
% data1 = load ('3-fc-d3-e.csv'); % Load data collected with Holter monitors
% fc = data1(:,3); %FLEXcon electrode data uses channel 3, in Volts
% data2 = load ('3-ag-d2-e.csv'); % Load data collected with Holter monitors
% ag = data2(:,3); %Ag/AgCl electrode data uses channel 3, in Volts
% fc= fc(1:24000); %Specified range of data for FLEXcon
% ag= ag(1:24000); %Specified range of data for Ag/AgCl
% All FLEXcon variables began with fc and Ag/AgCl variables with ag %
%% The Number of Samples per 1 second and
                  %the duration of the signal with time vector
%Fs=200;  % Biopac system sampling frequency
Fs=180;   % Holter monitor sampling frequency
dt=1/Fs;  % time step between each sample
duration=length(fc)*dt; % the duration of data in seconds (2 minutes)
t=0:dt:duration-dt; % The vector of time
t=t';   % it changes teh columns to rows
%% Detrending solution
%N=200; % 1 second long for detrending of Biopac system
N=180;  % 1 second long for detrending of Holter monitors
for i=1:N:length(fc)-N-1
p1=polyfit(t(i:(i+N-1)),fc(i:(i+N-1)),1); % Coefficients for FLEXcon
polynomial
yfit1=polyval(p1,t(i:(i+N-1)));
p2=polyfit(t(i:(i+N-1)),ag(i:(i+N-1)),1); % Coefficients for Ag/AgCl
polynomial
yfit2=polyval(p2,t(i:(i+N-1)));
for j=1:N
fc(i+j-1)=fc(i+j-1)-yfit1(j); % FLEXcon detrended of raw signal
ag(i+j-1)=ag(i+j-1)-yfit2(j); % Ag/AgCl detrended of raw signal
end
end
%% Remove the DC noise of the signal
fc=fc-mean(fc); %FLEXcon signal
ag=ag-mean(ag); %Ag/AgCl signal

%% Plots the Raw data after removing DC noise.
figure(1)
plot(t,fc); % Plots FLEXcon signal
grid on; hold on;
plot(t,ag, 'r-.');  % Plots Ag/AgCl signal
xlabel('Time [s]');
ylabel('Voltage [V]');
title('Raw ECG Waveform');
legend('FLEXcon','AgCl');
%% Low-pass filter
bl=[1 0 0 0 0 0 -2 0 0 0 0 0 1]; % Coefficients b of the difference equation
of low-pass filter
al=[1 -2 1]; % Coefficients a of the difference equation of low-pass filter
fc_lp=filter(bl,al,fc); %FLEXcon low-pass filter
ag_lp=filter(bl,al,ag); %Ag/AgCl low-pass filter
```

```
%% High-pass filter
bh=[-1 zeros(1,15) 32 zeros(1,15) 1]; % Coefficients b of the difference
equation of high-pass filter
ah=[1 1]; % Coefficients a of the difference equation of high-pass filter
fc_hp=filter(bh,ah,fc_lp); %FLEXcon high-pass filter
ag_hp=filter(bh,ah,ag_lp); %Ag/AgCl high-pass filter
figure (2)
plot(t,fc_hp); %FLEXcon signal after band-pass filter
grid on; hold on;
plot(t,ag_hp, 'r-.'); %Ag/AgCl signal after band-pass filter
xlabel('Time [s]');
ylabel('Voltage [V]');
title(' Bandpass Filter of ECG Waveform');
legend('FLEXcon','AgCl');

%% Derivative filtering, squaring
bd=(1/8)*[2 1 0 -1 -2]; % Coefficients b of the difference equation of
derivative function
ad=[1]; % Coefficients a of the difference equation of derivative function
fc_der=filter(bd,ad, fc_hp); %FLEXcon derivative filter
ag_der=filter(bd,ad, ag_hp); %Ag/AgCl Derivative filter
fc_sq=(fc_der).^2; %FLEXcon, signal squared of derivation
ag_sq=(ag_der).^2; %Ag/AgCl, signal squared of derivation

%% Moving average filter
N=30;
bm=(1/N)*[ones(1,N)];
am=[1];
fc_m=filter(bm,am,fc_sq); %FLEXcon Moving Average filter
ag_m=filter(bm,am,ag_sq); %Ag/AgCl Moving Average filter
figure(3)
plot(t,fc_m);
xlabel('Time (s)');ylabel('Voltage (V)');
title('FLEXcon ECG Waveform for Moving Average Filtering');
figure(4)
plot(t,ag_m, 'r');
xlabel('Time (s)');ylabel('Voltage (V)');
title('AgCl ECG Waveform for Moving Average Filtering');
%% Thresholds set by the mean of MA signal
thr_fc= mean(fc_m); %Threshold for FLEXcon signal is set by the mean of MA
thr_ag= mean(ag_m);%Threshold for Ag/AgCl signal is set by the mean of MA
fc_p=zeros(size(fc_m));%Sets all values below threshold to zero for FLEXcon
ag_p=zeros(size(ag_m));%Sets all values below threshold to zero for Ag/AgCl
fc_p(find(fc_m>=thr_fc))=1; %All values above threshold are 1 for FLEXcon
ag_p(find(ag_m>=thr_ag))=1; %All values above threshold are 1 for Ag/AgCl
figure(5)
plot(t,fc_p)
hold on; grid on;
plot(t,ag_p, 'r-.');
xlabel('Time [s]');
ylabel('Amplitude [filt V]');
title('Square ECG Peak Waveform');
legend('FLEXcon','AgCl');
%% searches for peaks between rising edges and falling edges
a1=diff(fc_p); %Derivative of square signal, FLEXcon
a2=diff(ag_p); %Derivative of square signal, Ag/AgCl
```

```
upindex_fc=find(a1==1); %Rising edges for FLEXcon
upindex_ag=find(a2==1); %Rising edges for Ag/AgCl
downindex1=find(a1==-1);%Falling edges for FLEXcon
downindex2=find(a2==-1); %Falling edges for Ag/AgCl
%% FLEXcon, peak detection
prev_peak_fc=0;
for i=1:min(length(upindex_fc),length(downindex1))
[amp1,indtemp1]=max(fc_hp(upindex_fc(i):downindex1(i)));
indmax1(i)=indtemp1+upindex_fc(i)-1;
rpeak_fc(i)=t(indmax1(i));
bpm_fc(i)=60./(rpeak_fc(i)-prev_peak_fc);
prev_peak_fc=rpeak_fc(i);
end
%% Ag/AgCl, peak detection
prev_peak_ag=0;
for i=1:min(length(upindex_ag),length(downindex2))
[amp2,indtemp2]=max(ag_hp(upindex_ag(i):downindex2(i)));
indmax2(i)=indtemp2+upindex_ag(i)-1;
rpeak_ag(i)=t(indmax2(i));
bpm_ag(i)=60./(rpeak_ag(i)-prev_peak_ag);
prev_peak_ag=rpeak_ag(i);
end

%% PD plots
figure(6)
plot(t, fc_hp)
hold on; grid on;
plot(rpeak_fc, fc_hp(indmax1),'or');
xlabel('Time (s)');ylabel('Voltage after BP filtering (V)');
title('FLEXcon ECG Waveform')
figure(7)
plot(t, ag_hp,'k')
hold on; grid on;
plot(rpeak_ag, ag_hp(indmax2),'xr');
xlabel('Time (s)');ylabel('Voltage after BP filtering (V)');
title('Ag/AgCl ECG Waveform')
%% Cubic interpolation of R-R interval
RR_fc=diff(rpeak_fc); %Difference in time between R-R intervals, FLEXcon
RR_ag=diff(rpeak_ag); %Difference in time between R-R intervals, Ag/AgCl
time_lr_fc=zeros(1,length(RR_fc));
time_lr_ag=zeros(1,length(RR_ag));
time_lr_fc(1)=0;
for i=2:length(RR_fc)
time_lr_fc(i)=sum(RR_fc(1:i-1));
end
time_lr_ag(1)=0;
for i=2:length(RR_ag)
time_lr_ag(i)=sum(RR_ag(1:i-1));
end
timeRR_fc=0:1/4:sum(RR_fc)-1/4;
timeRR_ag=0:1/4:sum(RR_ag)-1/4;
ys_fc=interp1(time_lr_fc,bpm_fc(1:length(time_lr_fc)),timeRR_fc,'spline');
ys_ag=interp1(time_lr_ag,bpm_ag(1:length(time_lr_ag)),timeRR_ag,'spline');
figure(8)
plot(timeRR_fc,ys_fc, 'b+-')
grid on; hold on;
plot(timeRR_ag,ys_ag,'r.-')
```

```
xlabel('Time [s]');
ylabel('Beats per Minute');
title('Cubic Interpolation of HR Time Intervals');
legend('FLEXcon cubic interpolation','AgCl cubic interpolation');
ys_fc= ys_fc-mean(ys_fc);
ys_ag= ys_ag-mean(ys_ag);

%% Power Spectral Density (PSD)
[psd_cubic_fc,f]=pwelch(ys_fc,length(ys_fc),[],512,4);
[psd_cubic_ag,f]=pwelch(ys_ag,length(ys_ag),[],512,4);
psd_cubic_fc=(abs(psd_cubic_fc)).^2;
psd_cubic_ag=(abs(psd_cubic_ag)).^2;
figure(9)
plot(f,psd_cubic_fc, 'LineWidth',3)
xlim([0 0.5])
grid on; hold on;
plot(f,psd_cubic_ag, 'r-.','LineWidth',3)
xlabel('Frequency in Hz');
ylabel('Power');
title('Representative Power Spectral Density Comparison');
legend('FLEXcon Electrodes','Ag/AgCl Electrodes')
%% LF/HF
low_index=find(f>=0.04 & f<=0.15);
low_f=f(low_index);
low_psd_cubic_fc=psd_cubic_fc(low_index);
low_psd_cubic_ag=psd_cubic_ag(low_index);
high_index= find(f>=0.15 & f<=0.4);
high_f=f(high_index);
high_psd_cubic_fc=psd_cubic_fc(high_index);
high_psd_cubic_ag=psd_cubic_ag(high_index);
NmuPeak_fc=length(rpeak_fc)
NmuPeak_ag=length(rpeak_ag)
LF_fc= sum(low_psd_cubic_fc)
LF_ag= sum(low_psd_cubic_ag)
HF_fc= sum(high_psd_cubic_fc)
HF_ag= sum(high_psd_cubic_ag)
LFHF_fc= LF_fc/HF_fc
LFHF_ag= LF_ag/HF_ag
%% Mean, Standard Deviation, RMSSD, SDNN
Energy_fc=sum((fc_hp).^2)
Energy_ag=sum((ag_hp).^2)
Power_fc =Energy_fc./(length(fc_hp))
Power_ag =Energy_ag./(length(ag_hp))
mean_bpm_fc= mean(bpm_fc)
mean_bpm_ag= mean(bpm_ag)
std_bpm_fc= std(bpm_fc)
std_bpm_ag= std(bpm_ag)
sumSD_fc=0;
sumSD_ag=0;
for i=2:1:length(RR_fc)
sumSD_fc= sumSD_fc+ ((RR_fc(i)-RR_fc(i-1))^2);
end
for i=2:1:length(RR_ag)
sumSD_ag= sumSD_ag+ ((RR_ag(i)-RR_ag(i-1))^2);
end
RMSSD_fc= sqrt(sumSD_fc./(length(RR_fc)-1))
```

```
RMSSD_ag= sqrt(sumSD_ag./(length(RR_ag)-1))
SDNN_fc= std(RR_fc)
SDNN_ag= std(RR_ag)
temp1=[LF_fc HF_fc;
    LF_ag HF_ag]
temp2=[LFHF_fc mean_bpm_fc std_bpm_fc RMSSD_fc SDNN_fc;
LFHF_ag mean_bpm_ag std_bpm_ag RMSSD_ag SDNN_ag]
```